Evaluation of the reform in the reimbursement system for TNF-inhibitors

An analysis of consumption and use of TNF-inhibitors

Silje Hobbel

Master thesis

Institute of Health Management and Health Economics

Faculty of Medicine

UNIVERSITETET I OSLO

15.05.2009

Acknowledgements

The work of this thesis started spring 2008. It has been an exciting and somehow long journey, which I will never forget!

There are a number of people who are entitled to an acknowledgement. First of all, I would also like to express my deep gratitude to my supervisor, Professor Terje P. Hagen at The Institute of Health Management and Health Economics for his constructive comments, patient supervisions and great feedback.

Further, I would like to thank Tord Bergesen for proofreading my thesis, and giving me useful comments. All my friends and fellow students over the years are in entitled of exceptional tanks. I would also like to give a special thank to my friends at the Institute, whom I have spent much time together with the last months, sharing both frustrations and pleasures. Thank you for bringing so much fun into this period.

Most of all I would like to thank my near and dear family, especially my parents, Ellen and Roger for always encouraging me, believing in me, and giving me their never ending support.

Finally, a special thanks goes to my dear Glenn, for helping with my thesis, and for bringing happiness to my life.

Silje Hobbel

Oslo, May 2009

Abstract

BACKGROUND: Tumor necrosis factor-alpha inhibitors and other biological inflammatory modifying pharmaceuticals are used among others within rheumatology. Some of the pharmaceuticals are given to the patients in hospitals through infusion, and others may be taken by the patients at home, through injection. These two pharmaceutical groups may replace each other in use, due to they fact that they are therapeutic equal. The financial responsibility for these pharmaceuticals was changed from 1 June 2006. Before this the financial arrangement for the pharmaceutical groups where divided: Norwegian Social Insurance Scheme financed home medication and hospital medication was finances by Regional Health Authorities.

OBJECTIVE: To analysis change in the financial responsibility of TNF-inhibitors, with the focus on if changes in relative prices as follow from transferring of the financial responsibility affect the use of home- versus hospital medications, and if transfer of the financial responsibility from have affected the total number of users.

METHODS: The method used in this thesis is multiple regression analysis. First, standard multiple regression and second a semi-logarithmic model.

RESULT: The main conclusion from this analysis is that the reform variable has a negative effect in the analysis, and one may say that the probability of receiving home medication has decreased after the reform, and that relative prices may be the current factor when physicians choosing between the pharmaceuticals. The relative use of home medication increased until 2006, and decreased from 2006-2007 with 5.18 percent. There are however quite large differences between regions, and it seems like patients in areas in Northern Norway have a lower probability of receiving home medication than others. When it comes to total consumption, the trend variable show that numbers of users has increased from 2004-2007, and that total consumption somewhat has decreased from 2006 to 2007, due to the negative reform variable.

CONCLUSION: We can with certainty say that there has been a shift from home medication to hospital medication after the change in the financial responsibility.

Abbrevation and acronyms

ABF	Activity based financing
AIP	Pharmacies maximum purchase price
AUP	Pharmacies retail price
BD	Bechterew's disease
DDD	Defined daily dosage
DMARDs	Disease modifying anti-rheumatic drugs
DRG	Diagnosis-related group
HF	Health Enterprise
HOD	Ministry of Health and Care services
JRA	Juvenile Rheumatoid Arthritis
LIS	Drug procurement cooperation
NBS	Norwegian Board of Health Supervision
NDP	Norwegian Prescription Database
NMA	The Norwegian Medicines Agency
NOK	Norwegian kroner
NPR	Norwegian patient register
NSAIDs	Non-steroidal anti-inflammatory drugs
NSD	Norwegian Social Science Data Services
NSI	The Norwegian Social Insurance Scheme
OLS	Ordinary Least Square
PsA	Psoriasis arthritis
R&D	Research and development
RA	Rheumatoid arthriti
RHF	Regional Health Authority
SPSS	Statistical package for social sciences
SSB	Statistics of Norway
TNF	Tumor necrosis factor alpha

Table of contents

1. Introduction

1.1 Approach to the problem

Tumor necrosis factor-alpha (TNF) inhibitors, and other biological inflammatory modifying pharmaceuticals[1], are used within rheumatology, gastroenterology and dermatology. Some of the pharmaceuticals are given to the patients in hospitals trough infusion, and others may be taken by the patients at home trough injection. Pharmaceuticals given in hospitals are in this thesis referred to as "hospital medication", and this pharmaceutical group consists of the pharmaceuticals Remicade, MabThera and Orencia (brandnames). The pharmaceuticals that may be taken at home are referred to as "home medication", and this group consists of Humira, Raptiva and Enbrel (brandnames). Among this, Enbrel and Remicade are the most frequently used, in fact these two pharmaceuticals has the highest trade of all pharmaceuticals in Norway, with respectively 3.5 and 2.5 percent of the total pharmaceutical market in 2007 (1).

Treatment with TNF-inhibitors is costly, and is estimated to be 100,000 – 150,000 NOK per patent annually. There has been a significant growth in the use of TNF-inhibitors recent years, e.g. the trade of Enbrel and Remicade increased with 12.7 percent and 13.9 percent from 2006-2007 (1).

Due to several arguments, the financing of TNF-inhibitors was transferred from the Norwegian Social Insurance Scheme (NSI) to the Regional Health Authorities (RHF) budgets from 1 June 2006.

Before 1 June 2006 the financial responsibility for the different pharmaceuticals was divided into treatment in hospital, and treatment at home, and the arrangements were as follows:

- Treatment carried out in the hospitals was charged from the hospitals budgets.
- Treatment carried out outside the hospital was financed by NSI trough the arrangement of reimbursement on blue prescription, after application from a physician (individual reimbursement after blåreseptforskriften § 10a)

[1] Further in this thesis the TNF-inhibitors and other biological pharmaceuticals will, just to simplify, be mentioned as TNF-inhibitors.

In a period, the hospitals had to partly finance Remicade, trough the block grants, while parts of the expenses where covered trough an arrangement of additional reimbursement, established particularly for this pharmaceutical (folketrygdloven §5-15), this applied only for Rheumatoid arthritis (RA) (2).

From 1 June 2006 all expenses associated with treatment of TNF-inhibitors charged the RHFs budgets. The transferring and the wish for neutrality between home- and hospital medication especially justified by a desire to (2):

- A more correct prioritization of the use of TNF-inhibitors and other pharmaceuticals used in opposition to the same conditions. The use of TNF-inhibitors should be subject to prioritizing in line with other treatment.

- Choice of pharmaceutical should be based on a medical and not economical background.

- Increased price competition between products.

In addition, the Norwegian Directorate of Health developed guidelines for the use of TNF-inhibitors, that should support the physicians right of prioritizing, including guidelines on which patients that should receive such treatment (2). Moreover, it should be noted that, among other things within a system of third-party financing, it is difficult to establish a real price competition between patented pharmaceuticals, despite the fact that the pharmaceuticals can replace each other in use. HODs assessment is that the funding established for the pharmaceuticals did not stimulate the real price competition (2).

When the government transferred the financing of TNF-inhibitors from NSI to RHFs budgets, they also transferred 404.2 million NOK to the block grants to cover the expenses. This was due to the increased spending for the health enterprises (HF), as a result of the reform. The HFs were given a budget increase equivalent to NSI's historical costs adjusted for expected growth. The allocation between the RHFs, occurred on the basis of historical costs distribution to the pharmaceuticals between the regions.

This study is part of a project on the evaluation of the changed funding for TNF-inhibitors, and is on commission by the HOD. The project was requested in order to find out how the new financing system for TNF-inhibitors works. In addition to this thesis, it is also performed two other analysis in the same project, of interest: "How are the national

guidelines for TNF-inhibitors implemented at department level in hospitals" by Karianne Orderdalen, and "Price competition in the market for TNF-α inhibitors in Norway" by Irina. V.P. Bjarkum

The transferring of the financial responsibility may have entailed several effects, both intentional and unintentional. This master thesis will be an evaluation of the reform in the reimbursement system for TNF-inhibitors, with the research question:

How has the change in the financial responsibility influenced consumption and use of TNF-inhibitors and other biological pharmaceuticals?

The focus of the paper is:

1) If changes in relative prices as follow from transferring of the financial responsibility affect the use of home- versus hospital medications.

2) If transfer of the financial responsibility from NSI to RHF, and with that from a reimbursement system to a system partly based on block grants, have affected the total number of users.

1.2 The pharmaceutical market

Expenditures for pharmaceuticals are increasing, and the total expenditure in 2007 was 17.4 billion NOK when looking at AUP. AUP is the pharmacies retail price, or in other words, the price that consumer must pay for the pharmaceuticals (3). This was a 3.4 percent increase from 2006, and almost a 40 percent increase from 1990 (3). The growth is largest within the group of pharmaceutical used in treatment of severe arthritis and some other immune related diseases. As mentioned, these pharmaceuticals are very costly pharmaceuticals, used by few patients (4). Earlier a lot of expenses were charged from the NSI, and the patient administrated medication at home. Still NSI is the largest pharmaceutical financing source, but because new, expensive and complex drugs has approached the market, patients are to a larger extent receiving pharmaceutical treatment through an out-patient stay, and the expenditures is charged from the RHFs budget.

The pharmaceutical market deviate from most other market for consumption goods. This applies both for the demand and the supply side. From the patient's point of view, demand for pharmaceuticals is characterised by low price elasticity. Price elasticity can be defined as the percentage change in quantity demanded of a good as the result of a percent change in price (5). The reason for this is that the patients are insured against medical expenses due to third-party payment. Third-party payment means that physicians choose medication on behalf of the patient on NSI's account. The physician will therefore be the decision maker regarding which pharmaceutical the patient shall receive. Demand for pharmaceuticals is also exposed to asymmetric information. Asymmetric information exist in a situation where the parties in a transaction have different information (5). In this case the physician have, often, more relevant and better information than the patient, and the patient is often abounded the physicians information. Supply for pharmaceuticals is linked to large expenses due to research and development (R&D). It is therefore important for authorities to regulate the pharmaceutical market so the characteristics mention regarding demand is taken care of, and arrangements like patents on pharmaceuticals exist so that the large expenses to R&D on the supply side not limits the development of new drugs.

1.3 Financing of pharmaceuticals

The grants from the central state to the hospitals consist of two parts. Activity based financing (ABF), meaning that the expenses reflect the activity, and revenues in block grants meaning it is independent from activity. Today, the activity-based reimbursement covers 40 percent of average costs, while block grant covers the remaining 60 percent. The activity-based reimbursement is based on Diagnoses-related group (DRG), which is a system that classify hospital cases into one of about 680 groups that are expected to have similar use of resources (6).

As a main rule, hospitals finance its own pharmaceutical use, both for in-and-outpatient stays, and it is free to the patient. If a patient is to use a pharmaceutical outside the institution, the physician may write out a blue prescription, given that the conditions are being met. Blue prescription is an arrangement for pharmaceuticals given to patents with severe, often chronic, conditions. The patients will only pay co-payments until a co-payment ceiling on 1,780 NOK, sat by NSI, is reached (7). NSI is the institution that covers all expenses to pharmaceuticals that are prescribed on blue prescription. Before 2000, all

pharmaceutical expenses was financed in the way described above; divided between pharmaceuticals used within and outside the hospitals. When TNF-inhibitors entered, there where difficulties regarding financial arrangements, and the government understood the system needed some changes.

In Ot.prp. nr. 83 (2001-2002) it is stated that medical technology develops faster than accessible resources, and because of this a gap exists between what is technical and economical possible. To limit this gap, it is important to make sure that the treatment is provided to the lowest possible costs to a given quality, in order to achievable treatment to a number of patients within the given limit of resource use. Understanding that there always will be a need to prioritize between different methods of treatment and between different groups of patients, it is vital to make sure that the priority is based on a well-documented foundation (8). Before the financial responsibility was transferred, it was the government's opinion that the divided financial responsibilities could lead to incentives for the hospital to prescribe Enbrel, which is given on blue prescription, in relation to Remicade, which was charged from their own budgets, and this again would lead to higher total costs for the society. The pharmaceutical use within the hospital is protected by economical incentives to negotiate discounts and choose the pharmaceutical with lowest price when choosing between two comparable pharmaceuticals. Because of this it was in 2000 established an individual arrangement due to financing of particularly expensive pharmaceuticals in those cases where there was a significant difference between the gross margin ratio in ABF and the average reimbursement. It was among other things established a temporary solution to the financing of Remicade. The hospitals had to partly finance Remicade through block grants. Further Remicade was also partly reimbursed through the arrangement that were established especially for this propose and partly through the arrangement of ABF (2). In this way, every treatment will then be a cost for the hospital. This may produce incentives for the hospital to undertake a trade-off between costs and utility for the pharmaceuticals in question. The hospital should prioritize use of the pharmaceutical next to other activity, and they will in larger extent be engaged to choose the cheapest pharmaceutical and this have, among others, led to the development of the Drug procurement cooperation (LIS), that approaches tender competition on a selection of pharmaceuticals (8). The Parliament decided that RHF should bear all costs due to TNF-inhibitors. 1 June 2006 the financial responsibility was transferred, and together with that, 404.2 million NOK was transferred to the block grants for covering the costs (2).

This was due to three arguments:

1. An absent price competition
2. Consumer distortion: physicians may no longer speculate in choosing a pharmaceutical that is not charged from the hospitals budget
3. Right priorities: the physicians will after the transferring have incentive to choose the right pharmaceutical for the patent without other considerations as e.g. price (9).

1.4 Theory

Resource allocation can be analysed within a demand framework. The basic assumption in this thesis that the physicians are decision makers, and act as the patient's agents. They decide which pharmaceutical to prescribe to the patient. However, physicians are not perfect agents, and they may have loyalties to trade-name drugs or to third-party payers (10).

Further we assume that hospitals prioritize between home- and hospital medication according to relative prices, supply side characteristics, as the hospitals revenue level, or number of specialists in rheumatology. Changes is relative prices is of particular interests since this directly can be related to the changes in financial regime. Until this date, hospitals net costs for RA patients eligible for TNF-inhibitors were related to outpatient visits. For patients receiving hospital medication costs related to the pharmaceutical were covered by the hospitals. For patients receiving home medication, NSI fully reimbursed the cost for the pharmaceuticals. In relative terms, this reimbursement may be regarded as a subsidy from NSI to the hospitals that affected the relative price the hospitals had to pay for the medications. Because of the subsidy, home medication was relatively cheaper for the hospitals than use of hospital medication. After transferring of the financial responsibility for home medications to the hospitals the subsidy disappeared, and this change is assumed to lead to a shift from home medication to hospital medication.

The revenue level of the hospitals in question are, apart from the share of revenues coming from the transfer of the price subsidy, given exogenously, and based on a model for distribution of the non-activity based income between the four RHFs in Norway. However,

the supply of services to RA patients will be affected by factors other than the hospital's revenue level, such as the labour market for rheumatologists. We assume that higher the supply of rheumatologist, the more patients will receive treatments. The last theoretical foundation that will be discussed is factors on the demand side, such as the patients travel distances to hospital and their age, where we assume that patients with long travel distance to hospitals will to a higher degree then people with short travel distance prefer home medication. The formal explanation will be elaborated in chapter 4.

1.5 Data and method

The data in this thesis is multi-levelled, with age groups (0-69, 70+) in a local government, local governments and HFs as the three levels. The age groups (level 1), lives in a local governments (level 2), and each local governments belongs to a hospital (level 3). The data on level 1 is referred to as cells, where cells describe the two age groups in a local government. Features of the local governments and the HFs, is respectively referred to as level 2 and level 3 data.

The data used in the analysis are collected from Norwegian patient register(NPR), which describe users of hospital medication, and Norwegian Prescription Database (NDP) that describe users of home medication. The data set consists of data from 2004-2007.

It was not possible to obtain data on individual level from NDP, and therefore we received data, describing number of patients in the two age groups (0-69 and 70+). As mentioned, these two age groups, referred to as cells, were measured on a local government level. The analysis unit is from this the two age groups within each local government, meaning that one local government consists of two cells (0-69 and 70+). In order for the NPR data to be useable, it was aggregated so it would be equivalent with the NDP data. The two files, NPR data and NDP data, where added together to form the dependent variables: Share home medication and Total consumption. Based on the patient's home municipality, the data was further linked to the structural variables. Structural variables are factors explaining the health status of a population, such as age groups and socio-economic variables. The last level of this analysis is HF level describing features with the hospitals. HF number is included as fixed effects dummies, to capture supply side effects.

Ideally, these data should be on patient level, but because of protection of personal policy to patients, this was not possible to provide for the current time. It would be better to also include data from 2008, but unfortunate this was not possible due to the time limit set for this thesis. As mentioned, the brand names of hospital medication included in the analysis are Remicade, MabThera and Orencia, and respectively for home medication Humira, Enbrel and Raptiva. Late in the process there was however discovered that MabThera and Raptiva not were transferred from NSI to the RHFs 1 June 2006, but 1 January 2008. This will most likely not affect the results since 2008 not is included, and because it was from 2004-2007 only 257 (0.45 percent) patients that received Raptiva.

The method used in this thesis is multiple regression analysis, which is used to explore the relationship between continuous dependent variables and a number of independent variables. The analysis estimates the effect of a variable X on a variable Y, where it is controlled for effects of other X-variables (11). To analyse the data there will be used two methods; First, standard multiple regression and second a semi-logarithmic model. Standard multiple regression is an analysis where all the dependent variables are entered into the equation simultaneously. The independent variables is separately evaluated in terms of its predictive power, over, and above offered by all the other explanatory variables (11).

1.6 Structure of the thesis

The thesis is organized as follows. The indications where TNF-inhibitors is used and how TNF-inhibitors work is explained in section two, while section 3 describes the institutional conditions. The theoretical background is described in section 4, followed by data, method and description of the empirical test in section 5. The results will be presented in section 6 and last, section 7 concludes the thesis.

2. Indications and treatment

2.1 Introduction

Chronic inflammatory diseases represent a substantial burden in social and economic terms of the Norwegian community. In this thesis there are the treatment liked to chronic inflammatory diseases related to rheumatology, dermatology and gastroenterology that will be studied. The most common within these groups are RA and Bechterew's disease (BD) psoriasis arthritis (PsA) and Crohn´s disease (12). The prevalence on rheumatoid arthritis (RA) alone is 0.5 to 2 percent (12, 13), and epidemiologic studies in Scandinavia have revealed a annual incidence of 25 per 100,000 (14). The diseases contribute importantly to the disease panorama in Norway, and causes untold suffering, economic loss and premature death (13). The short-term therapeutic goal is to relieve symptoms and improve function by reducing inflammation. This is done to achieve the long-term goal which is to stop or slow progression of damage, improve functional health status and reduce mortality (14). Treatment based on pharmacological strategies is of increasing significance in the management of inflammatory diseases including the use of several novel medicines. Patients with inflammatory diseases must often try out different pharmaceuticals before they find the optimal treatment (12, 13). The drugs used to treat inflammatory diseases of the musculoskeletal system can be divided into two main classes; symptomatic modifying drugs and disease modifying anti-rheumatic drugs (DMARDs). The symptomatic modifying drugs, like non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids, may relieve symptoms such as pain, stiffness and swelling, but most likely in the absence of interfering with the underlying disease mechanisms. DMARDs are believed to interact with the basic disease processes and are able to reduce or delay the development of functional loss and irreversible injury caused by the disease. There are however many patients without satisfactory effects from these drugs, especially after long-term use. Treatment with biological drugs, such as TNF- inhibitors is an alternative for these patients (13). In this chapter inflammation will be described, followed by description of the diseases and treatment of the diseases that is treated with TNF-inhibitors. In table 1 and 2 the pharmaceuticals included in the analysis will be laid out.

2.2 What is inflammation?

Inflammation is a basic process where the body defends itself against infection with bacteria and viruses, irritation and injuries and involves immunological mechanisms. In certain diseases, however, the body's immune system inappropriately triggers an inflammatory response when there are no foreign substances to fight off. Cytokines, which are mediators involved in transferring signals between different cells in the immune system can either accentuate the inflammation processes or slow it down. The balance between stimulating cytokines and those with a subduing effect is believed to be of critical importance (12). Inflammatory diseases will affect this balance and the uninhibited inflammatory balance directed against the body's own tissue (12).

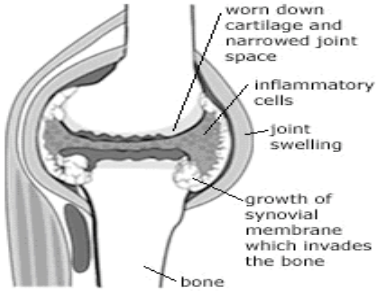


Figure 1 Inflammation in joints

In inflammatory diseases, the body's normally protective immune system causes damage to its own tissues. The body responds as if normal tissues are infected or by some means abnormal (15). The symptoms are different in inflammatory bowel diseases and rheumatic diseases. When inflammation occurs, several mediators from the body's white blood cells are released into the blood or affected tissues leading to various responses including increased blood flow to the area, swelling, redness and warmth. The inflammatory process may stimulate nerves and cause pain for example, in joints (12).

Inflammatory diseases is in some cases difficult to diagnose, and are only appointed after a careful evaluation of complete medical history and physical exam. There are a number of treatment options for inflammatory diseases including medications, rest, exercise and surgery (15).

2.3 Rheumatic inflammatory diseases

RA is the most common inflammatory disease in Norway. The prevalence is about 0.5 percent, and it affects three times as many women as men (16, 17). For most of the patients the disease starts in the hands or feet with rigidity, tenderness or pain. Some of the joints get swollen, and show signs on inflammation. In early disease phase some of the persons may note some tiredness, loss of appetite, weight reduction and fever (16). The disease may develop over several years. The inflammatory process attacks the joints producing synovitis that further may progress to destruction of articular cartilage. Evolvement of diminished mobility results from these disease mechanisms. It is however only 10 percent of the diseased patients with RA that will lead to total disablement (16).

Juvenile Rheumatoid Arthritis (JRA), which is arthritis in childhood, is a chronic disease that is known by continuous inflammation in the joint. The clinical picture is the same as for RA. JRA is a rare disease that only affects about 100 of 100,000 children, i.e. approximately 1,000 children under 16 years have JRA in Norway (18).

BD is a disease in joints, which have similarities with RA, but BD is known more frequently among men than women. The prevalence is about 0.3 to 0.1 percent (19). The first symptoms usually occur in the age group 20-30 years. There is stiffening of the spinal joints and ligaments, so that movement becomes increasingly difficult and painfully. It can result in bony alkylosis of the vertebral joint. The stiffening may extend to the ribs and limit the suppleness of the rib cage, so that breathing is impaired (20). The cause is unknown, but have considerable connection with histocompatibility antigen HLA-B27 (in more than 90 percent of patients with this disease) [11]. The patient is diagnosed through a combination of clinical history and X-rays, and it is often difficult to confirm a diagnosis. Most patients respond well to medications given to reduce pain and inflammation, combined with exercises (20).

About 1.5 percent of the Norwegian population suffer from psoriasis, and 7 percent of these gets PsA, thus the prevalence is about 0.1 percent. There is no evidence that indicates that one sex will be more frequently affected than the other. Patients of all ages can be affected, but it is most common between age group 20 to 40 years (12). PsA is an inflammatory joint disease in combination with psoriasis skin disease. The arthritis in PsA may take various clinical forms, including subgroups resembling RA or BD disease. The cause of PsA is unacquainted. However, it is known that PsA is not a communicable disease, but persons can

receive some genetic quality from parents which can dispose for PsA (12). 75 percent of the patients will first get manifestations of the skin disease, and subsequently develop the arthritis. The diagnosis psoriasis should be made by a dermatologist, while the inflammation in joints by a specialist in rheumatology. PsA is treated in the same way as RA, but there are other drugs as a first choice (21).

2.4 Inflammatory bowel diseases

Crohn's disease and ulcerative colitis (UC) are chronic inflammation and their precise cause is not known. Crohn's is a transmutral disease which may affect all layers in the gastrointestinal tract as well as any part from mouth to anus (20). UC is primarily limited to colon, but may affect the lower part of the small intestine. It may in some cases be difficult to determine which of the diseases the patient has, because the clinical picture might be relatively similar (22). The disease occurs when the immune system attacks the gastrointestinal tract. The symptoms of Crohn´s and UC may vary significantly, but the main symptoms are abdominal pain, diarrhoea, vomiting, or weight loss. The diseases can also cause complications outside the gastrointestinal tract, such as skin inflammation of the eye and rashes, arthritis (20).

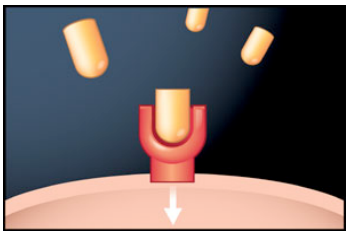
2.5 Treatment

Biological drugs represent a relatively novel strategy of treating inflammatory diseases. It can be described as medicines derived from living organisms that target specific receptors in the immune system. With most of the patients the treatment will fast moderate the inflammation, and the pain will be reduced. TNF is a cytokine that acts as an inflammatory agent as described above regarding inflammation. TNF-inhibitors block this cytokine and helps reduce pain – usually after one to two weeks after the treatment starts. The treatment can suspend inflammation, and prevent injury, but are only effective as long as the patient take the drug (23). Biologics is given as infusion during a couple of hours at a inpatient ward or as injections, which the patient takes at home (12).

Treatment with the pharmaceuticals in the analysis is all monoclonal antibody therapy, but they can be divided in three groups (TNF-inhibitors, Immunosuppressants and Antineoplastic agents), because they work slightly different. Currently there are three

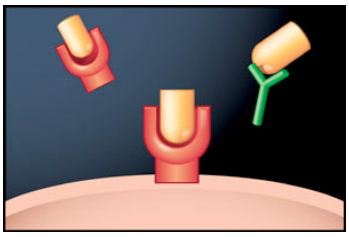
available TNF-inhibitors on the market (brand name in brackets): adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade). Equal to TNF-inhibitors there are three other pharmaceutical used for the same indications: abatacept (Orencia), efalizumab (Raptiva) and rituximab (Mabthera). Raptiva is a recombinant humanized monoclonal antibody; Orencia is a selective costimulation modulator as it inhibits the costimulation of T- cells, and Mabthera is a chimerical monoclonal antibody. The marketing license for Raptiva was suspended from the market 19 February 2009, the risk of serious side effects is considered to be greater than the benefits. However, Raptiva will be included in the analysis.

2.5.1 How does Biologics work?



Inflammation in joints involves activation of immune system attacking the bodies' own cells. This happens when an inflammatory substance bind to a receptor in the surface of the cell, and elicit an inflammatory response.

The inflammation can be naturalized as follows:



The biological drug can unite to the inflammatory substance, so it is impossible for the substance to unite to the recipient on the surface of the cell. This takes place using pharmaceuticals, which either is antobodies (Remicade/Humira), or constitute a forged recipient substance (Enbrel).

2.5.2 Pharmaceuticals included in the analysis

Table 1 Description of home medication included in the analysis

INJECTION home medication				
ATC	*Substance*	*Brand name*	*Indication (01.07.08)*	*First- and second choice for indications from the guidelines*
L04AB04/L04AA17	Adalimumab	Humira	RA, PsA, BD, CD	First: Crohn's Second: BD and PsA
L04AB01/L04AA11/ L04AB01	Etanercept	Enbrel	RA, PsA, BD	First: BD, PsA Second: RA, Psoriasis
L04AA21	Efalizumab	Raptiva	PsA	First: Psoriasis

Table 2 Description of hospital medication included in the analysis

IFUSION hospital medication				
ATC	*Substance*	*Brand name*	*Indication (01.07.08)*	*First- and second choice for indications*
L04AB02	Infliksimab	Remicade	RA, PsA and BD	First: RA Second: Crohn's, ulcerative colitis
L01X C02	Rituximab	MabThera	RA	First: RA (for patients who have had to stop with Remicade or Enbrel because of the lack of effect or side effects)
L04A A24	Abatacept	Orencia	RA	First: RA (for patients who have had to stop with Remicade or Enbrel or MabThera because of the lack of effect or side effects)

3. Instututional conditions

3.1 Introduction

The pharmaceutical market deviates from most other markets for consumption goods and several central assumptions for a competitive market are not fulfilled. The way the pharmaceutical market deviate applies both for the supply- and demand side in the market (24). The supply side is characterised by market power due to the patent system, and price inelastic demand because of third-party payments and asymmetric information. Most countries regulate prices on prescription drugs as a result of this. This introduces a trade-off between low prices and incentive for R&D of new pharmaceuticals, is an example of what kind of problem the demand side can meet. The development of piece systems and governmental rules must be well-considered resolutions (25). This chapter will be a description of the features by the pharmaceuticals market, such as the demand and supply side. Further on, pharmaceutical policy and regulation mechanism will be presented. The purchaser-provider relationship and how pharmaceuticals are financed will be brought about, before the new financing system for TNF-inhibitors and the background for this.

3.1.1 Trade of pharmaceuticals

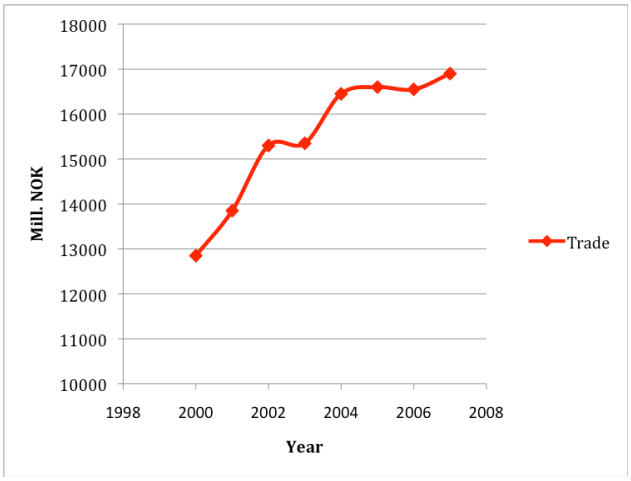


Figure 2, trade of pharmaceuticals in Norway, adjusted to 2007 NOK. Source LMI.

The total trade of pharmaceutical was in 2007 16.9 billion NOK AUP. Compared to the trade in 2000 this is a 76 percent increase of the consumption of pharmaceuticals (fixed costs) (3, 26).

The strong growth in consumption of pharmaceuticals is an international trend. Pharmaceuticals constitute constantly an increasing part of the total health expenditures, which was around 10 percent in Norway in 2003. Even if there have been a strong growth in the consumption (fixed prices), Norway is still among the OECD countries that uses the lowest amount, when it comes to pharmaceutical expenses as a share of total health expenditures and consumption of pharmaceuticals per inhabitant (26, 27). A considerable part of this growth is due to development of new and expensive drugs. The growth has decreased after 2006. This is due to discontinued patents and that prices on pharmaceuticals have in general decreased (3).

3.2 Features by the market for pharmaceuticals

3.2.1 Demand and supply side

The demand for pharmaceuticals is in general known by low piece elasticity. This means that the demand for pharmaceuticals responds relatively modest on price changes, and there is more than one reason for this. First, patients are to a large extent insured against expenses on prescription drugs, due to third-party payment, which imply that the consumer pays a small share of the total price and the government are responsible for reimburse the remaining trough different arrangements. This imply that the market for prescription drugs is characterised by third-party payments, where the patients only pays co-payments for the pharmaceuticals (25). Prices will therefore not be relevant in situations where a patient can choose between pharmaceuticals. Second, it is not only the patients that can choose between different pharmaceuticals, due to the position the physicians has as prescriber of pharmaceuticals and a large extent of asymmetric information in the market (25). Asymmetric information can be described as a situation where one party has more or better information than the other. Even if a physician gives a patient a choice between two or more substitutable pharmaceuticals, the patient if often abounded the information and recommendations from the physician. It is also the physician that decides quantity and dosage of the prescribed drug. In reality it is often the physician that make resolutions on

behalf of the patient (25). It is not obvious that the physician is the perfect agent for the patient, especially with a view to that the physician can be exposed to promotion from the pharmaceutical industry and it is not given that the physician have perfect information about product prices (25). Both large amount of third-party payments, and the fact that the physicians behave as (imperfect) agents for the patents contribute to that the demand for prescription drugs is extremely little sensitive to prices. The physicians behave, however, not only as agent for the patients, but also for the governments, that wants a cost-efficient prescribing practice from the physicians. In this way the governments meet a classical principal-agent problem regarding physicians prescription of pharmaceuticals (25). In Norway the pharmacies may undertake generic substitution, which imply that they can distribute (cheaper) generic substitutes to the pharmaceutical that are prescribed. In this way the pharmacies also behave as an actor on the demand side in the market. The demand for pharmaceuticals is determined usually as interaction between consumers (the patients), physicians, the governments and pharmacies (25).

The market for pharmaceuticals is known by certain special characteristics on the supply side. Expenses by produce pharmaceuticals consist in a large part of costs linked to (R&D) of new pharmaceuticals. There costs can be large, but when a new pharmaceutical first is developed and approved for use, the costs by producing the pharmaceutical is relatively low. The production of the pharmaceutical is accordingly characterized by high fixed costs and low marginal costs. This means that prices over marginal production costs is essential to cover the costs by R&D. Due to high fixed costs, the conditions for a good functional competitive market is not present. To secure that the industry has incentives to use resources on development of new pharmaceuticals, this is protected by a patent arrangement that gives a monopoly on production and sale of new, approved pharmaceuticals for a limited period of time. By giving the firms that develop a new pharmaceutical the opportunity to set a price that exceed marginal production costs for a given period of time, and with that profit on the expenses linked to the de development of the new pharmaceutical, incentives for future investments in R&D will be taken care of (25).

3.3 Pharmaceutical policy

The market for pharmaceuticals is, as mentioned above, known by a very inelastic demand and a considerable extent of market power on the supply side. A market without regulation

may therefore lead to extremely high prices, especially for pharmaceuticals with patents (25). Because of this, a lot of countries, including Norway have introduced regulation regimes in this market. From the government's point of view, choice of regulation gear depends on the object of the regulation (25). In Norway the superior goal of the Norwegian pharmaceutical policy is the right use of pharmaceuticals, both medically and financially. Patients should have access to secure equal and effective pharmaceuticals, regardless of ability to meet payments, and the prices shall be as low as possible. If one looks at the organisation of the administration, HOD has the main responsibility for developing the pharmaceutical policy. The ministry has delegated responsibility to other organs such as NMA, Norwegian Board of Health Supervision and NSI. NMA is a national regulatory authority that approves pharmaceuticals. They inform about effect, side effects, price and terms for blue prescription, and monitor clinical testing. NSI has the responsibility for reimbursement and social security. The reimbursement arrangements shall be in line with the superior goal with secure equal and effective pharmaceuticals, regardless of ability to meet payments. The pharmacies shall secure proper distribution of pharmaceuticals and cooperate to the right use of pharmaceuticals (28).

3.3.1 Regulation

The pharmaceutical industry is one of the most heavily regulated of all industries (29). The government regulates the pharmaceutical market through a number of reforms, so the public expenditures on pharmaceuticals are somewhat under control. The regulation of the pharmacies purchase price (AIP), which is the price from wholesalers to pharmacies, is one of these reforms. In addition, the government has decided how large profit the pharmacies may add to AIP. This means that the prices from pharmacies to patients and NSI also are regulated (AUP) (30). The pharmacies may freely trade pharmaceuticals to a lower price than maximum AUP, but in practice the pharmaceuticals with patent are sold to the maximum price, which also is the price NSI reimburses. NMA determines AIP that is the mean of the three lowest prices on a certain pharmaceutical, in a selection of 9 countries in Europe. The Norwegian prices revise if the prices calculated from changes, or if the currency changes considerably. The prices are not changed more than once a year (30).

Parallel import of pharmaceuticals was allowed from 1 January 1995, and was a consequence of regulation about free marketing from EU. Price differences on pharmaceuticals in EEA develop the basis for a parallel import market of pharmaceuticals. Parallel import parts from direct import in the sense that the importers do not have any other connection with the producers than buying products from them. The parallel importers buy pharmaceuticals from countries where the prices are low in EU/EEA and resale the pharmaceuticals in countries where the prices are high after changing the gaskets and gasket attachment. Price differences between counties are attributed to different regulation for determine maximum price and development in foreign exchange (24). The parallel imported pharmaceuticals' share of total distribution has decreased in the last two years. This may be explained by the decrease of prices on pharmaceuticals and that pharmaceutical prices in Norway is on a generally lower level compared to the rest of Europe (3).

In a therapeutic reference price system all pharmaceutical gaskets that can be counted for therapeutic equal are gathered in one group. One tax reference price is defined for their pharmaceuticals, usually the lowest price in the group, which is the amount NSI reimburses irrespective of choice of pharmaceutical (31). The patients must pay the shim if they prefer a pharmaceutical with a higher price than the tax reference price. However, the physician may make exceptions if there are medical reasons for this, so that the patients do not get charged additional expenditure. The tax reference price system was mainly developed to stimulate reduction in prices within generics, where grouping, equal doses and range of use are often uncomplicated. Therapeutic equal pharmaceuticals have somehow different goals than the tax reference price. The goal in a reference price system is to stimulate medical and economical right choice of medicament. For therapeutic equal pharmaceuticals there may be lack of information regarding documentation that unambiguously supports the facts about which doses give the same effect and that this formulate the foundation for accurate calculations of price. In addition, several of the pharmaceuticals in the treatment group may also be used for other conditions. This may in turn lead to twists in the competition on other treatment areas than the tax reference price system intended (31).

In 2001, the reform on generic substitution in pharmacies became operative. This, together with discontinued patents and the introduction of stage price system for pricing of substitutable pharmaceuticals, contributed to an increase of the share of generics. The last years has seen an considerable increase in the number of generics. After the patent on the

trade name expired, other producers are allowed to produce duplicates (generics) with the same chemical substance as the trade name (3). The pharmaceutical is usually protected 8 – 12 years after they entered the market. When the patent time expires and several equal pharmaceuticals are on the market this should stimulate to competition and reduced prices, because the suppliers compete about offers and pharmaceuticals that can substitute each other.

The pharmacies may, together with LIS, which is achieving collective bargaining, reduce prices on pharmaceuticals. The RHFs have made an agreement regarding purchasing pharmaceuticals, and the designation of this agreement is LIS. The purpose of LIS is to complete contracts on purchasing, and delivery of pharmaceuticals, and other pharmacy goods after commission from HFs, and with that reduce the costs of these products. LIS catches up tenders on all pharmaceuticals used in HFs (32). LIS has reported that through tender competition they got a price reduction on 7.4 to 36.5 percent on four different TNF-inhibitors from March - October 2007 (4). The pharmacies have, however, weak incentives to conduct the discounts because of the problems mentioned above. To secure that patients and NSI receive the highest possible discount, the stage price model and the profit sharing model has been developed (30).

In January 2005, the government introduced the step-price system. The system was introduced with the intention of lowering prices and increasing the use of generics. When there is competition between generics, the chemical substance can be included in the step-price system and receive a step price. The step price is a percentage share of the total price the pharmaceutical had before generic substitution. Generic competition has lead to a 30 percent price reduction. The prices are again reduced with 55 percent and 75 percent after 6 months, depending on how large distribution the generic substitution had when the generic competition occurred. The stage price model applies for certain pharmaceuticals, and for those, the stage price is the maximal price NSI reimburses. The pharmacies must offer at leas one pharmaceutical (from the pharmaceuticals with same chemical substance) to stage price. This also applies for the pharmaceuticals on white prescription where the patient pays for the pharmaceuticals (30).

The profit share model shall give the pharmacies an incentive to negotiate purchase prices. If a pharmacy achieves lower prices than determined AIP, the pharmacies may keep up to half

of the discount. The profit share model was introduced in 1995. The new pharmacies legislation in 2001 gave wholesalers the right to own pharmacies and constitute chain-stores (30). Today over 70 percent of the pharmacies are integrated with wholesalers, and the profit share model will therefore not be efficient. The arrangement will, however, still be significant for independent pharmacies (30) .

3.4 Pharmaceutical expenses

About two thirds of the pharmaceutical expenses are financed by the public sector, because public sector reimburses expenses for pharmaceutical prescribed on blue prescription and pharmaceuticals used in hospitals and nursing homes (3). The total share that is reimbursed through blue prescription has decreased, and the parts that are financed by RHFs budgets have increased somewhat the last two years. The private part of the financing consists of the patients' expenses on drugs without prescription and prescription drugs on white prescription as well as co-payments on blue prescription. The ceiling for co-payments, i.e. the maximum amount of expenses patients' shall pay for visits at physicians and medication on blue prescription trough one year was 1,780 NOK in 2009 (7). The reason pharmaceutical expenses have flattened out is patent expiring, stage prices and preferred pharmaceuticals (3). There has been a reduction in the pharmaceutical expenses covered by NSI the last years, and some of the reason for this is, among others, the transferring of TNF-inhibitors from NSI to RHFs (3).

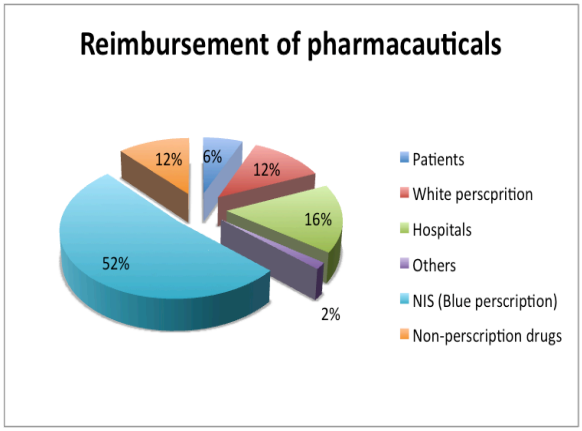


Figure 3, financing of the pharmaceutical market. Source LMI

The public sector finances about 70 percent of the pharmaceutical expenses. The greater part

of this is through reimbursements on blue prescription. From 2005-2006 this share have yet decreased from 55.7 to 51.8 percent. The share that is financed through the hospitals budgets has, however, in the same period increased from 12.4 percent in 2005 to 16.5 in 2006. This is because of the transferring of TNF-inhibitors from NIS to RHFs budgets (3).

3.5 The reimbursement system

3.5.1 Purchaser-provider relations

Integrated purchaser–provider relations are the dominant feature of the health care system. The interaction between the central state, RHFs and HFs are to a certain degree based on a purchaser–provider division since the RHFs purchase health services and the HFs provide the specialist health services. Furthermore, the central state owns the RHFs, and the RHFs own the health enterprises and are thereby responsible for the state's provider function. The RHFs draw up the guidelines on the needs to be covered and ensure that those needs are followed up through their steering and ordering functions (27).

The hospitals are financed through grants from central state dependent upon the number of patient's treated, the patients' DRG's, and a national standardized cost per treatment to hospitals. The financing system consists of two parts, ABF and block grants. ABF covers today 40 percent of average costs, while block grant covers the rest (6, 27). The RHFs are free to set up their own system to fund the HFs. So far, research has shown that the RHFs do not reallocate the ABF funding from the state. It is, though, a principle that the prospective payment scheme is an arrangement between the RHFs and the state. The block grant contribution is allocated from the region to the health enterprise based on their resource needs, e.g. based on age structure in the area (27).

3.5.2 Financing of pharmaceuticals

Pharmaceuticals are financed in two ways: the specialist health care services finances, as a main rule, pharmaceuticals used within the sector and pharmaceuticals prescribed by a physician is, as a main rule, financed by NSI through blue prescription. There are, however, some important exceptions from this that will be elaborated later. The local governments cover all costs for pharmaceutical to patients in nursing homes and institutions. For patients outside this regulation whose pharmaceuticals have been given the right to be reimbursed

through Blue prescription, the pharmaceutical expenses are covered by NSI, if the (28). The arrangement of blue prescription is a proportional reimbursement system with a cost ceiling for co-payments. As mentioned, this implies that the patients only pay co-payments for a given percentage of the total costs, while NSI covers the remaining through the same regulation. The regulation of reimbursement on blue prescription has a general regulation §9, that states that pharmaceuticals on a given medication list are to be reimbursed by NSI, and a individual regulation, §3a, that gives patients reimbursement from NSI after a individual application (28).

3.5.3 A new financing system for the pharmaceuticals in question.

Different funding of the therapeutic comparable pharmaceuticals Remicade and Enbrel highlighted a need for a more flexible funding for pharmaceuticals that are used within and outside hospital. The arrangement applies for all the pharmaceuticals included in the analysis. Remicade, MabThera and Orencia are used exclusively within the hospital and are financed by the hospitals; this group of pharmaceuticals will further in the thesis be mentioned as hospital medication, while Enbrel, Humira and Raptiva will be mentioned as home medication. Home medication is initiated in the hospital, but later taken by the patient at home. It was earlier reimbursed by NSI through blue prescription. The differences in the financing responsibilities for the pharmaceuticals may in some cases likely have a determined effect for the hospitals choice between the pharmaceuticals for treating the patients, and may, in total, lead to higher pharmaceutical expenses for the public sector (8). In 2000, an individual arrangement was established due to financing of particularly expensive pharmaceuticals in those cases where there is a significant difference between the coverage in ABF and the average reimbursement (8). Among others it was established a temporary financial arrangement for Remicade as day treatment. Against this background, each treatment would normally be a cost for the hospital. It helps that the hospitals have incentives to make a trade-off between the benefits and costs of the selection of pharmaceutical. The hospitals had to finance Remicade partly through block grants. Further Remicade were reimbursed through the arrangement that where established specially for this purpose, and last partly through ABF (2). From June 2006 the financial responsibility for TNF inhibitors and other biological pharmaceuticals were transferred entirely to RHF. The contents of this change were that the hospitals also got the financial responsibility when the patients administrate treatment with the current pharmaceuticals outside the hospital (8). The

argument for this change is mentioned in the next section. The pharmaceuticals in question constituted 40 per cent of the expenses on individual refunding (8).

3.5.4 Background for the changed financing system

The main reason for transferring TNF-inhibitors was that the government experienced that the different financing methods likely constitute a vital importance in the choice between the pharmaceuticals, and this led to increased pharmaceuticals expenditures for the society (8). The Ot.prp 83 (2001-2002) states that NMA has, based on international guidelines for treatment, calculated that about 4000 patients will need treatment with TNF-inhibitors, and from a medical point of view it is assumed that about 50 per cent can be treated with hospital medication, and the other half with home medication (8). The home medication is, as mentioned, taken as injection twice by the patient at home, while hospital medication is given as infusion about 6 times a year, and this infusion has to be handled by physicians or nurses and the patient must stay in the hospital for observation in a couple of hours after the treatment is finished (8). The government states that there is reason to believe that different financing methods isolated gave the hospital intensives to choose home medication in preference to the therapeutic comparable pharmaceuticals in the hospital medication group, which often have a lower price (8). The reason for this is that the home medication is prescribed and distributed through blue prescription, while hospital medication is financed through RHFs budgets, i.e. Remicade debits the RHFs budgets, while Enbrel debits NSI's budget (8). The pharmaceuticals used within the hospital are protected by economical incentives to negotiate discounts, and for the physicians to choose the pharmaceutical with lowest price if two comparable pharmaceuticals can be used to treat the patient. Because of this it was, as mentioned in the previous section, in 2000 established an individual arrangement due to financing of particularly expensive pharmaceuticals in those cases where there were a significant difference between the coverage in ABF and the average reimbursement (8), and from June 2006 the RHF got the full financial responsibility for financing TNF-inhibitors.

The argument for the transferring was tripartite:

- Consumption distortion: when the pharmaceuticals charges different budgets, this may lead to physicians making choice on witch pharmaceutical to give the patient on behalf of this.

- Right priorities: The physicians working in hospitals have the best qualification to make right priorities when it comes to treatment of patients with pharmaceuticals needing injections in proportion to pharmaceuticals needing infusion. The physicians will have an improved basis to make these priorities when the pharmaceuticals are charged the same budget.
- Absent price competition. There is no price competition between the pharmaceuticals, even if they are medical equal, because of the financing through NSI and the use of different reimbursement methods. The transferring will give equal reimbursement methods, and stimulate to price competition (9).

4. Theoretical fundation

4.1 Introduction

The problems addressed in this thesis are if the change in the financial responsibility of TNF-inhibitors has led to a change in use or consumption of the TNF-inhibitors. The following conditions will be explored further:

1) If changes in relative prices as follow from transferring of the financial responsibility affect the use of home- versus hospital medications.

2) If transfer of the financial responsibility from NSI to RHF, and with that from a reimbursement system to a system partly based on block grants, have affected the total number of users.

Resource allocation can be analysed within a demand framework, as explained by Halsteinli et.al (33). The basic assumption in this analysis is that physicians are decision makers acting as the patient's agents. Further problems addressed in this section are based on the assumption that hospitals prioritize between home and hospital medication according to relative prices, supply side characteristics as the hospitals revenue level, or number of specialist in rheumatology and factors on the demand side as the patients' travel distances to hospitals and their age.

Changes in relative prices will be of particular interest since this directly can be related to the changes in financial regime from 1 June 2006. Until this date, hospitals net costs for RA patients eligible for TNF-inhibitors were related to outpatient visits. For patients receiving Remicade additional costs related to the drug were covered by the hospitals.[2] For patients receiving home medication like Enbrel, NSI fully reimbursed the cost for the pharmaceuticals. In relative terms, this reimbursement may be regarded as a subsidy from NSI to the hospitals that affected the relative price the hospitals had to pay for the medications. Because of the subsidy, home medication was relatively cheaper for the hospitals than use of Remicade. After transferring of the financial responsibility for home medications to the hospitals the subsidy disappeared. This chapter starts out by discussing

[2] Some of the costs for Remicade were covered as a side payment to the activity based funding system.

how this shift in relative prices for the two types of medication should affect the hospitals' choices, and is followed by how other factors may affect the choice between home and hospital medications.

4.2 Physicians as decision makers

In a free market equilibrium, demand can be measured through the consumers' willingness to pay. The pharmaceutical market deviates from this ideal model, both by introducing a physician as an agent for the consumers and by heavy subsidies, often full third-party payments for the medication (34).

Consumption and use of TNF-inhibitors may be understood as a decision-making problem, where the physician act as the patient's agent and decides which pharmaceutical to prescribe to the patient. However, physicians are not perfect agents for the patients, but do also have loyalties to e.g. producers of trade name drugs or to third-party payers (10). In a way physicians can be said to act as double or tripple agents, both as an agent for the patients, the insurance providers and the producers. Lundin (2000) does, however, conclude that there are reasons to believe that the physician acts more as the patient's agent than as an agent for the public sector (10). This assumption will be followed in the following chapter.

4.3 Income and substitution effects

We assume that the physician wishes to maximize the utility of the patients under the condition of supply side restrictions, here describes by a budget restriction.

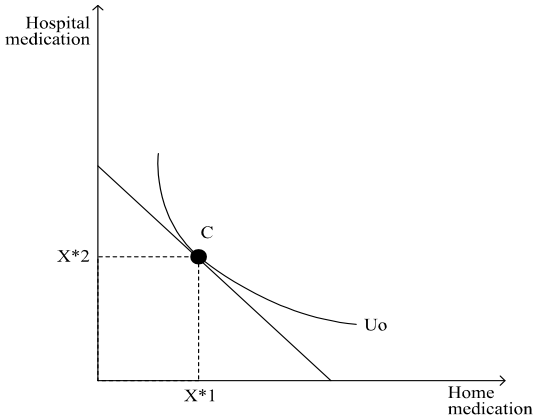


Figure 4, the budget constraint

In figure 4, the number of patients receiving home medications is described on the x-axis, while the number of patients receiving hospital medications is described on the y-axis. The figure further shows how a hospital, C, chooses between home- and hospital medication for their patients. The choices must be done within the hospitals budget constraint, meaning that the number of patients receiving home medications times the price for receiving home treatment plus the number of patients receiving hospital medications times the price for receiving hospital treatment adds up to the available budget.

P1x1+p2x2 = m,

Where p1 is number of patients receiving home medication, x1 is the price for receiving home medication, p2 is number of receiving hospital medication and x2 is the price for receiving hospital treatment, and m is the available budget.

The curve U is the indifference curve that shows the utility of the two goods, home- and hospital medication. Its utility is constant along the indifference curve, and shows how much the hospital have to increase the consumption of hospital medication with when they reduce the consumption of home medication with one unit to keep the utility constant (5).

Hospital C may for example treat for 2200 patients with hospital medication and 1600 with home medication. The slope of the budget constraints shows what the trade-offs are. A movement one unit along the horizontal axis from i.e. 1600 patients treated to 1601 patients treated would reduce the number of patient treated in hospital. This holds even if the price for home medications is close to zero for the hospitals as there are other costs related to this treatment. The amount of home medication a hospital "must use" to purchase home medication is determined by the relative prices of the two alternatives, and it is illustrated as in the figure above by the slope of the budgets constraint.

The maximization problem

A change in price or income will change the demand for home medication and hospital medication.

Further we assume that the hospital wishes to use all its income, and consume on the budget line. The budget line will therefore have the slope $x_2 = \frac{m}{p_2} - \frac{p_1}{p_2} x_1$.

Solpe: $-\frac{p_1}{p_2}$, and intersects the y-axis $\frac{m}{p_2}$

The following maximization problem will occur:

$\underset{x_1,x_2}{Max}$ U= $U(x_1,x_2)$ in subject to $p_1x_1 + p_2x_2 = m$

This can be solved using Lagrange-method:

L=U $(x_1x_2) - \lambda(p_1x_1 + p_2x_2 - m)$

The first order conditions:

$$\frac{\partial L}{\partial x_1} = \frac{\partial u}{\partial x_1} - \lambda p_1 = 0 \qquad \text{i)}$$

$$\frac{\partial L}{\partial x_2} = \frac{\partial u}{\partial x_2} - \lambda p_2 = 0 \qquad \text{ii)}$$

$$\frac{\partial L}{\partial \lambda} = p_1x_1 + p_2x_2 - m = 0 \qquad \text{iii)}$$

Equation i) is divided on ii), and we will find that optimal slope of the indifference curve, equals the slope of the budget line; they are tangents to each other.

$$\frac{\frac{\partial u}{\partial x_1}}{\frac{\partial u}{\partial x_2}} = \frac{p_1}{p_2} \quad \leftrightarrow \quad -\frac{\frac{\partial u}{\partial x_1}}{\frac{\partial u}{\partial x_2}} = -\frac{p_1}{p_2} = MRS$$

MRS is the marginal rate of substitution, and it tells how much x2 have to increase when x1 is reduced with one unit (substitute) in order to keep the utility on a constant level.
The demand function for the two goods home medication and hospital medication can be found from:

$x_1^* = x_1(p_1,p_2,m),\ x_2^* = x_2(p_1,p_2,m),$

x_1^* and x_2^* is demand in optimum. See also figure 4 where, where optimum is presented graphically.

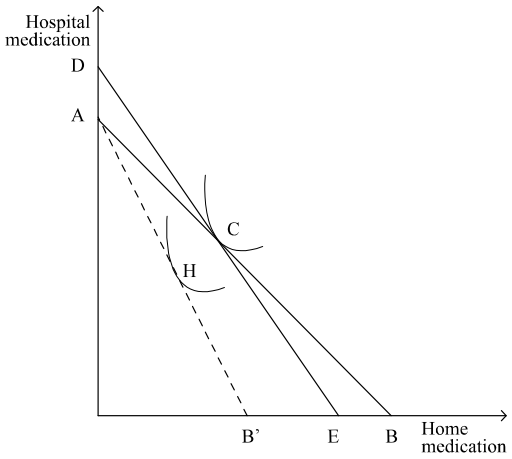


Figure 5, income and substitution effect

Let us now assume that the price for home medications p1 increases for the hospital as will be the case as the financial responsibility of TNF-inhibitors are moved from NSI to the RHFs. Two different effects will then appear: a substitution and an income effect. The substitution effect can be described as a change in consumption on the basis of a change in relative prices of a good (5), and the income effect as the change in quantity demanded that result from a change in real income (29). As in the previous figure, the vertical axis in figure 5 shows the number of patients receiving hospital medication, while the number of patients receiving home medication is represented by the horizontal axis. The line AB is the budget constraint. The starting point is in C where $p_1x_1 + p_2x_2 = m$. The budget line has the slope $-\frac{p_1}{p_2}$, and intersects the x-axis in $\frac{m}{p_1}$ and the y-axis in $\frac{m}{p_2}$. The indifference curve and the budget line tangents in the point C. This point shows the actual allocation between home- and hospital medication before the changes in prices. If the entire revenue is used on hospital medication the hospital will place itself in A, and at the corresponding point B if all recourses are used on home medication. The slope of the budget line AB expresses the relative cost relationship between home- and hospital medication as in figure 4. When NSI financed home medication they reimbursed the actual cost of the pharmaceutical, while the hospital was responsibility for costs regarding consultation et cetera, and the reimbursement from NSI may therefore be seen as a subsidy to the hospitals. When the financial responsibility was transferred, the subsidy for home medication was removed and the hospitals got the responsibility for covering all the costs linked to the pharmaceuticals. This,

in turn, lead to a change in the relative prices; home medication became relatively more expensive for the hospital.

When the relative price on home medication increased the budget line shift inwards. Since p1 has increased, the budget line will intersect the x-axis in a lower value of x1 than before. At the same time we observe that the budget line has become steeper. The increase in p1 (home medication) has led to that the relative price on home medication is higher, thus $-\frac{p_1}{p_2}\uparrow$. We will now have new equilibrium there the new budget line AB' tangents the indifference curve in the point H. The substitution effect show that the relative price on home medication and hospital medication has changed (p1/p2). The hospital wishes to substitute away from home medication, which has become relatively more expensive, and towards hospital medication, which is relatively cheaper. They will now use the same amount of hospital medication, but the use of home medication is reduces due to the removed subsidy.

However, at the same time as the prices shifted, the governments transferred 404.2 million NOK to RHFs block grant to cover the increased expenses on TNF-inhibitors that appeared as a result of the removal of the subsidy. In the figure, this is indicated as an outward shift in the budget line. This means that the hospitals revenues increased, and from the theory of microeconomics, one knows that when an individual's income increases, he can spend more money on consumption of goods. The increased income is illustrated with a parallel shift to the right from AB´ to DE. The adaption in C is the effect of the increased income. The hospital can now adapt in a point with the same utility as before the relative price on home medication increased. In this new situation the hospitals treat the same number of patients as before, but due to the changes in relative prices, it may be argued that the hospitals find it more cost-efficient to use more resources on patients treated in hospital than patients treated at home.
This line of reasoning generate two hypothesis:

H1: The changes in financial responsibility and thereby relative prices will lead to a shift from home medications to hospital medications

H2: The number of patients treated will be unaffected by the changes in financial responsibility.

4.4 Supply side

The revenue level of the hospitals in question are, apart from the share of revenues coming from the transfer of the price subsidy, given exogenously, and based on a model for distribution of the non-activity based income between the four RHFs in Norway. The system is described in NOU 2008:2 and is divided in two. Revenue in the block grants is independent from activity, while revenue via ABF and outpatient care is based on activity. The block grants are based on formulas including variables describing need for specialist health care services such as health criteria's, socio-economic criteria's and criteria's that capture aspects related to climate and latitude (35).

Based on the block grant the RHFs allocate resources to the specific hospital. However, the supply of services to RA patients will be affected by factors other than the hospital's revenue level, such as the labour market for rheumatologists. In the empirical part of the thesis the supply side by number of rheumatologist (by 10000 inhabitants) will be described. Based on the model described above the hypothesis is:

H3: The higher the supply of rheumatologist, the more patients will receive treatments.

4.5 Patients preferences

If the patient could choose if they wanted to take the medication at home or in the hospital, they might have relatively different preferences regarding choice of pharmaceutical.

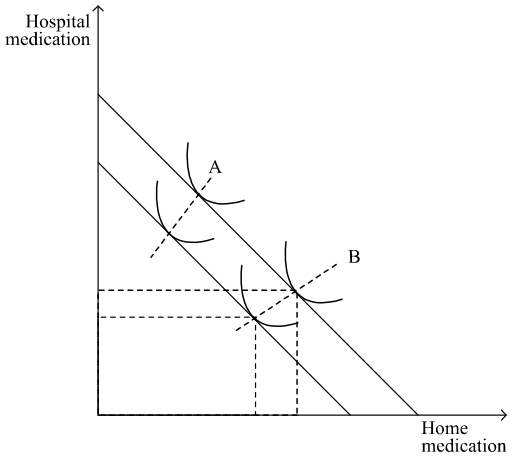


Figure 6, patients preferences

As described previous in this chapter physicians act as an agent for patents and take their preferences into account. There are two assumptions regarding this that will be explained further. The first is in terms of travel distance, where the assumption is that patients living far from the hospitals have stronger preferences for receiving home medication, i.e due to long travel time and time off work. People with short travel distance to hospitals are assumed to be more indifferent regarding choice of pharmaceutical. In figure 6, A and B depict expansion paths for patients with different travel distances to the nearest hospital. A has a short travel distance while B has a long travel distance. The hypothesis is:

H4: Patients with long travel distances to hospitals will to a higher degree than people with short travel distances prefer home medication.

Patients' preferences regarding age can be explained from the same figure. The assumption here is that young people will have stronger preferences on receiving home medication. The fact that older people, at least pensioners, usually have more time, and are not away from work may explain this finding. When it comes to age, A is patients with high age, and B patients with low age. Based on the patient's preferences the probability for a patient to receive hospital medication increases with the patient's age.

H5: Patients who work will to a higher degree than people who are pensioners prefer home medication, thus patients with high age will prefer hospital treatment.

4.6 Other factors affecting place of treatment

In addition to this specific hypothesis we test out effects of variables describing needs at local governments level, such as age structure, number of disabled and level of education. We do not have any specific hypothesis regarding these variables that will further be described in the next chapter.

5. Data and method

5.1 Introduction

The data material in this analysis is collected from several sources, and the data is analysed on three levels. Cells-level, local government level and HF level. The linear regression analysis examines the relation between dependent variables and independent variables. The analysis estimates the coefficients of a linear equation that best predicts the value of the dependent variable. Regression analysis has certain assumptions that have to be met. If the conditions are not met, the results may be biased. The starting point in the research was first to analyse weather the changes in the financial responsibility had influenced consumption and use of TNF-inhibitors. Further on, there are two problems that will be investigated. First, whether the total consumption of TNF-inhibitors increased after the reform, and second, whether the distribution between home- and hospital medication has changed. In this chapter the levels in the analysis and the data collection will first be presented, followed by operationalization of variables and descriptive statistics. Last, the multiple regression analysis, the empirical model and the assumptions for the model will be presented.

5.2 Data

5.2.1 Multi-level analysis

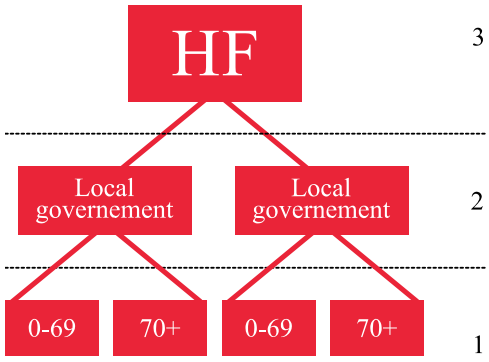


Figure 7, multi-level analysis

The data in this thesis is multi-levelled, with age groups (0-69, 70+) within a local government, local governments and HFs as the three levels. The age groups (level 1), lives in a local governments (level 2), and each local governments belongs to a hospital (level 3).

The data on level 1 is referred to as cells, describing the two age groups in local governments. This will be explained further. Features of the local governments and the HFs, is respectively referred to as level 2 and level 3 data.

The data used in the analysis are collected from two sources. The data that describe users of hospital medication is collected from secondary sources from the NPR. These data consist of variables about hospital medication that describe whether the patents have received TNF-inhibitors either as in- or outpatient treatment. These data were collected from DRG-reporting; on encoding rules explain to us by Bjørn-Yngvar Nordvåg, shown in table v1 in the appendix. Further, the data describing users of home medication was collected from NPD, also from secondary sources. NDP consists of data about dispensed drugs in Norway, and from the data we could find out how many patients that have received home medication on blue prescription. The data set consisted of data from 2004-2007.

Due to private personal policy towards patients, it was not possible to obtain data on individual level from NDP, and therefore we received data, describing number of patients in the two age groups (0-69 and 70+). These two age groups, referred to as cells, were measured on a local government level. The analysis unit is from this the two age groups within each local government, meaning that one local government consists of two cells (0-69 and 70+).

The reason why cell-level was selected is because it is closer to an individual level than a local government level. A cell-level explains variance in the independent variables measured at a lowest possible level. This reduces the possible correlation between variables describing the use and supply side variables. Secondly, the data includes many observations, and thus provides a good information base to discover the relationships between consumption and demand variables.

In order for the NPR data to be useable, it was aggregated so it would be equivalent with the NDP data.

The two files, NPR data and NDP data, where added together to form the dependent variables: Share home medication and Total consumption (see chapter 5.3.1 for further explanation).

Based on the patients' home municipality, the data was further linked to structural variables. Structural variables are factors explaining the health status of a population, such as age groups and socio-economic variables. Data on structural variables was found in Statistics of Norway (SSB) and The Norwegian Social Science Data Services (NSD). In the analyses the structural variables that were used was primarily information about the travel distance to the nearest hospital where patients were treated with TNF-inhibitors, and socioeconomic variables, such as age groups, disabled, unemployed, income and education. Travel distance was calculated using a matrix containing travel distances from municipality to municipality. Which hospital the patients were assumed to travel to, was based on an overview from SAMDATA where local government were grouped together in residence areas, and indicate which hospital that belong to this area (36).

The last level of this analysis is HF level describing features with the hospitals. HF number is included as fixed effects dummies to capture supply side effects.

Ideally, the NDP data should be on patient level, but because of protection of personal policy to patients, this was not possible to provide for the current time. We did not get information on local governments where the number of users where less than 5, due to the same argument. The NDP data was therefore estimated from defined daily dosage (DDD), for every cell in the data set. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (37). It would be better to also include data from 2008, but unfortunate this was not possible due to the time limit set for this thesis.

Since the analysis covers more than one level, the probability for making specification mistakes is less than in models with only one unit, where it is impossible to investigate casual heterogeneity.

After an application to Norwegian social science data service, they found that the project with the variables, patients' home municipality, sex and age in two age groups 0-69 and 70+, does not need permission. The data is selected on the basis of the drugs in table 1 and 2. The data's used to analyze the consumption was measured at local government level. The data set consists of 431valid local governments, but due to some outliers 4 local governments had to be excluded**.**

Further on we focus on rheumatology due to RA is the only indication that has been approved for the pharmaceuticals the whole period. The other indications (gastroenterology and dermatology) were approved at different times in the period 2004-2007.

5.3 Operationalization of variables

5.3.1 Dependent variables

Table 3, operationalization of dependent variables

Name on variable	Description	Construction
Share home medication	Measures the probability of receiving home medication in relation to total number of patients that have received TNF-inhibitors	(Patients receiving home medication /(patients receiving home medication +patients receiving hospital medication))
Log Share home medication		Ln (Share "home medication")
Total consumption	Measures number of patients receiving either home- or hospital medication in relation to the total population	((Patients receiving home medication + patients receiving hospital medication)/inhabitants)
Log Total consumption		Ln (Total consumption)

Table 4, descriptive statistics for dependent variables

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Share "home medication"	2742	.00	1.00	.4567	.37165
Log Share "home medication"	2223	-5.49	.00	-.8386	.84880
Total consumption	3268	.00	.02	.0018	.00237
Log Total consumption	2639	-12.78	-3.72	-6.6900	1.21848
Valid N (listwise)	2219				

From the descriptive statistics, the variable Share home medication show that 45.67 percent of the patients receiving TNF-inhibitors receives home medication. The variable Total consumption, can be interpreted in the same way, 0.18 percent of the inhabitants receive TNF-inhibitors. The prevalence on RA alone is 0.5 to 2 percent, meaning that a number of 2400-9600 persons in Norway have this disease. From total consumption we can calculate that the mean of persons in Norway that have received TNF-inhibitors annually from 2004-2007 was 8640.

5.3.2 Independent variables

Table 5, operonalization of independent variables

Variable	Operationalization	Data source
Trend	Time trend variable.	
Reform	Dummy variable that describe the reform. It takes the value 0 for 2004-2006 (before the financial regime), and 1 for 2007 (after the financial regime.	
Age	Dummy variable that takes the value 0 if patient's age is 0-69 and 1 if patient's age is 70+.	
Gross income	Describing individual mean income in a local government	SSB
Avst_rauma	Travel distance from local government to the nearest hospital that provides treatment with TNF-inhibitors, in kilometres. Calculated from matrixes.	Information on which local government that belongs to each hospital was found at SAMDATA.
Share disabled	(disabled/inhabitants)*100	SSB and NSD
Share_edu	Share of inhabitants with primary school as the highest level of education. (grunnskole/inhabitants)*100	SSB
Share unemployed	Unemployed, ((aledkv+aledmen)/inhabitants)*100	SSB and NSD
Share 20-66	People in age group 20-66, (age20_66/inhabitants)*100	SSB
Share 67-80+	People in age group 67-80_, (age67_80_/inhabitants)*100	SSB
Share number of specialists in raumatology	Number of specialists in rheumatology in relation to hospitals that provide treatment with TNF-inhibitors. (antall_rau/inhabitants)*100	Legeforeningen, list over specialists and their occupation.

Table 6, descriptive statistics for independent variables

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
age	3457	0	1	.50	.500
Gross income	3392	186366.67	494600.00	259864.8238	32901.35594
Avst_Reuma	3392	.00	858.30	129.3604	142.32656
Share disabled	3406	2.46	12.84	6.8783	1.92243
Share_edu	3392	13.63	49.58	28.2514	5.69133
Share number spesialist in rheumatology	3424	.0047	6.7797	.349172	.5519286
Share 20-66	3424	52.04	66.96	58.5706	2.34984
Share 67-80+	3424	6.58	25.03	15.1937	3.29506
Share unemployed	3406	.24	6.38	1.4027	.74177
Valid N (listwise)	3392				

The descriptive statistics show quite large differences between the local governments. For example, the share of elderly varied between 6.5 percent and 25.5 percent, and travel distance varied from 0 kilometres to 858.3 kilometres. Share of education varied between 13.63 percent and 49.58 percent, as well as share of unemployed, where there in some local governments was 0.24 percent unemployed and 6.38 in one other. The mean was however 1.4 percent, which means that there was at least one local government where a larger share of the population was unemployed. When it comes to share number of specialists in rheumatology in the local governments this varied from 0.0047 to 6.78 percent, the mean was, however, 0.35 percent.

5.4 Method

The object of this analysis is to find out if, and how, the consumption of TNF-inhibitors has changed after the implementation of the financial regime in 2006. The analysis used is multiple regression analysis in Statistical package for social sciences (SPSS) 16.0.

5.4.1 Multiple regression analysis

Multiple regression analyses are used to explore the relationship between continuous dependent variables and a number of independent variables. The analysis estimates the effect of a variable X on a variable Y, where it is controlled for effects of other X-variables (11). To analyse the data there will be used two methods. First, standard multiple regression and second a semi-logarithmic model. Standard multiple regression is an analysis where all the dependent variables are entered into the equation simultaneously. The independent variables are separately evaluated in terms of its predictive power, both over and above offered by all the other explanatory variables (11).

The second method is a semi-logarithmic model. This model is an analysis where the dependent variables are transformed into logarithms. Given that the multiple regression analyses assume normally distributed scores, as will be explained further in the assumptions for the analysis, one alternative was to transform the dependent variables, which where quite skewed, into logarithms. This means to mathematically modify the scores using a formula until the distribution looks more normal. Logarithmic transformations of the dependent variables have a number of practical applications in the regression analysis, among others

that the effect can be interpreted as the percentage change in the Y-variable by a measurement unit change in independent variable (11). The interpretation is somehow a bit more complicated after the dependent variable is logarithmic transformed, as the estimates is raised in 2.7 (the natural logarithm).

Empirical model

The following model is specified:

P_{ijk} is the dependent variable which describe Share home medication, accordingly probability for a patient to receive home medication and Total consumption, accordingly how many persons that have received TNF-inhibitors, for a individual (cell 0-69, 70+) *i* from a local government *j* and belonging to hospital *k*.

$$P_{ijk} = b_0 + b_1 C_{ij} + b_2 G_{ij} + b_3 S_j + b_4 Y_k + e_{ijk} + u_{0jk} + v_{0k} \quad (1)$$

Where b_0 is a constant term, C_{ij} is a vector of individual characteristics (age 0-69, 70+), G_{ij} is a vector that describe characteristics by the local government (such as income and education), S_j is vector describes share of specialists in rheumatology and travel time to the hospital and Y_k is a dummy variable describing characteristics with the unit that prescribe the pharmaceutical (the dummies will capture supply side effects, and work as fixed effects).

Fixed effects

In addition to the included variables, the consumption of TNF-inhibitors could be determined by other variables, such as efficiency, routines or “culture” in the hospital. The general supply level of services within the individual HF, or hospital is assumed to have effect on the consumption of health services - the larger provision of services thus larger use (11). Since the income to the HFs largely is determined by demographic and socioeconomic factors and inclusion of income level as explanatory factor, get an endogenous element among the explanatory variables. To avoid this, dummy variables are included for 17 HFs to model the supply side. The dummies will mainly capture supply side effects apart from share of specialists in rheumatology and travel distance that are already included, but can also capture excluded explanatory variables. When dummy variables are used in this manner, a fixed effect analysis is performed, which exploits variation both in the dependent and

independent variables within hospital areas (38). Fixed effects at hospital level, which is a vector of 0/1 dummy variables for each of 17 hospitals that offer treatment with TNF-inhibitors, was applied to the analysis. The included hospitals, which are fixed effects where based on a list from "Norwegian association in Rheumatology" containing all hospitals in Norway with potential to treat patients with TNF-inhibitors.

Assumptions of multiple regression analysis

Using the multiple regression method is convenient because of its properties. In the justification for that the assumptions of a multiple regression analysis is presented. There is a set of assumptions about the variables we attended to be included in the analysis that need to be fulfilled in order to trust the results. It is not possible to test all assumptions for regression, as for example, if all relevant x variables is included in the analysis, or if expected value of standard error is zero, however will the assumptions that can be tested for are presented under (11).

There are a set of assumptions about the variables that need to be fulfilled in order to included them in the analysis, the assumptions are related to sample size, normally distributed residuals, absence of heteroskedasticity, multicollinearity and singularity, and the data set need to be checked for outliers.

In order for the data to be generalisable it is important that the sample size is large enough (11). The analysis consists of 431 valid local governments. Each local government is divided in into age groups 0-69 and 70+ thus generating cells. The division into cells was done on all data from 2004-2007, which means that the data set consists of approximately 3448 cells. This is considered as a large data set, so there will be no problems with the generalisability.

The assumption for normality may be checked in a p-p plot. It is fulfilled if the residuals are in a straight diagonal line. The dependent variables Share home medication and Total consumption are somewhat off the diagonal line in the p-p plot, but the logarithmic variables have a better fit to the line. When it comes to the independent variables they have a quite good fit to the line, except number of specialist and travel distance. When these variables are explored they have a skewness and kurtosis on respectively 5.3 and 45.0 for travel distance, and 8.6 and 2.7 for number of specialists. The skewness value provides an indication of the symmetry of the distribution, and kurtosis about the "peakedness" of the distribution. If the distribution are perfectly normal the value should be 0, and we see that the values these two

variables show is quite far from this. When the variables are logarithmic transformed, the values decrease to nearby 0 for both variables. However, the original variables will be kept due to that information may be lost, because the places that have 0 km of travel distance to nearest hospital, or the local government that do not have specialists in rheumatology will be omitted.

A sequence or a vector of random variables is heteroskedastic if the variables have different variance. The ideal is that the model is homoskedastic that is that the variance of residual in a regression is the same for all values of x-variables. The scattering on the standard error will then be the same for all combinations of the observed x-values. Homoskedastic is ensured through inclusion of fixed effects.

Multicollinearity exists when the independent variables are strong correlated, this may lead to biased results (11). Multicollinearity can be checked by consider the Person correlation (r). The value indicates the strength of the relationship between the independent variables, and the value may range from -1.00 to 1.00. A value of 0 indicates no relationship at all, and a value of 1.0 and -1.0 indicate perfect positive and negative correlation. The values in this analysis set the limit of correlation at 0.75 (-0.75). A Pearson correlation, and there was correlation between the unemployed women and men, and the variables were therefore computed to one variable – unemployed. Singularity occurs when the independent variables are actually a combination of each other, e.g. one age group from 0-69, and another from 67-80+. Because of perfect co-linearity between the groups 0-19, 20-66 and 67-80+, 0-19 is not included in the analysis.

The data set has been checked for outliers by computing histograms, and the maximum and minimum values has been checked, and there were outliers in the variable disabled in local governments: 1144, 1151, 1739 and 1835. These governments were therefore removed from the data set.

6. Results

6.1 Introduction

The starting point for the thesis was to analyse the effect of a change in the financing responsibility of TNF-inhibitors. Available for the analysis a total number of 57,496.53 patients receiving TNF-inhibitors was included, distributed as follows: 20,849.53 patients receiving home medication and 36,647 patients receiving hospital medication was included, and further computed into the dependent variables Share home medication and Total consumption. First a multiple regression, and seconds a semi-logarithmic model was performed. The probability for a patient to receive home medication will be presented first and second the probability for receiving TNF-inhibitors. A full set of estimates is presented in table 7. In addition, the estimate from the fixed effects is presented in table v6 in the appendix.

6.2 Variation in total consumption of TNF-inhibitors

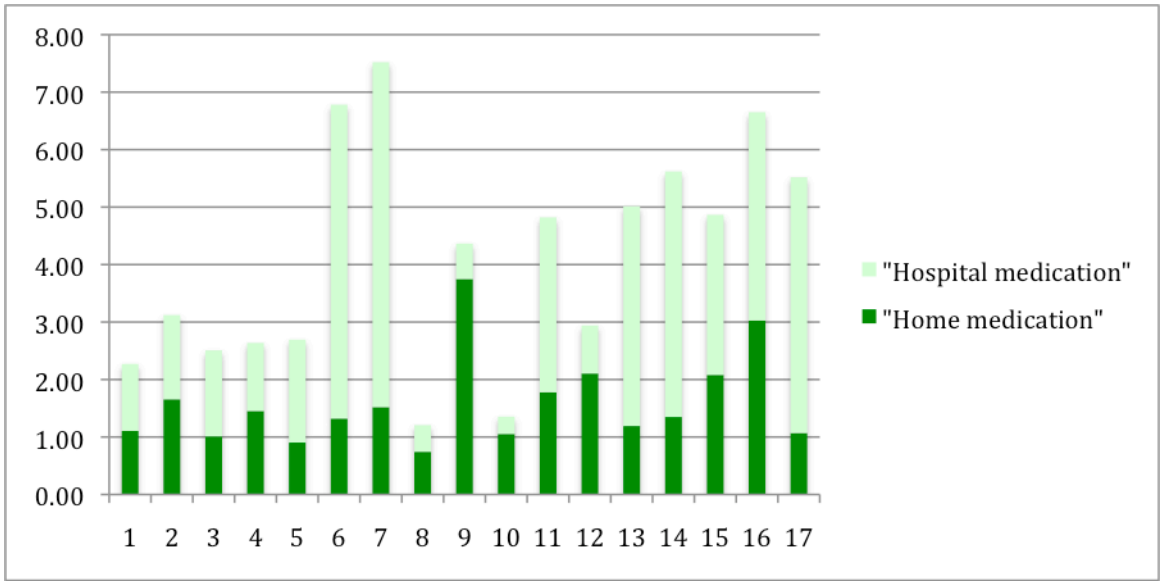


Figure 8, users per 1,000 inhabitants in 2007

The figure presents how many persons that have received home- and hospital medication in 2007. The horizontal axis represents the different hospitals distributing TNF-inhibitors, hospital ID is presented in table v2 in the appendix, and the vertical presents number of patients. The numbers are standardises in relation to numbers of inhabitants in the local

government belonging to the hospital, and multiplied with 1,000. Actual use of home- and hospital medication after hospital ID is presented in table v3 in the appendix. Total numbers of patients that have received TNF-inhibitors from 2004-2007 were 57,496.53 distributed as follows: 20,849.53 received treatment at home, and 36,647 received treatment in hospital. This means that 36.26 percent of the patients received home medication in this period. The total consumption was highest at the hospitals Betanien, Buskerud and Norlandssykehuset, while the lowest consumption was at Sørlandet hospital. The highest consumption of hospital medication was also at the hospitals Buskerud, Betanien and in the University Hospital in Nord-Norge (UNN), while the highest consumption of home medication was at Stavanger hospital and Norlandssykehuset.

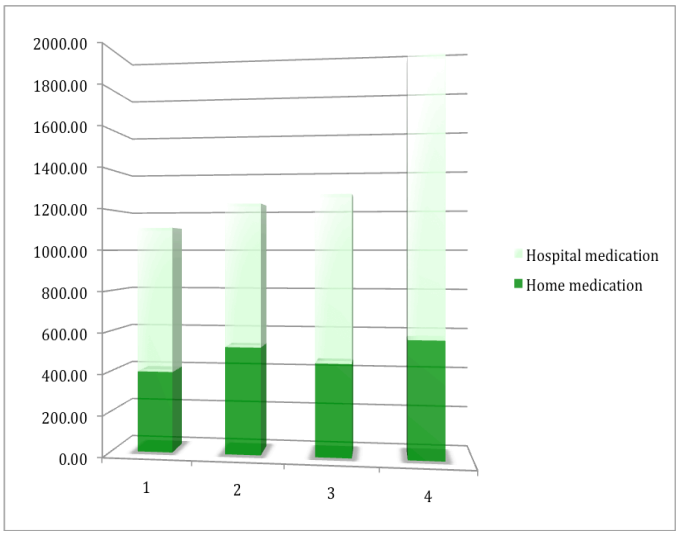


Figure 9, users in Health regions per 100,000.

Figure 9 percents how many persons that have received home- and hospital medication. The horizontal axis represents the four RHFs, where 1 is South- Eastern Norway Regional Health Authority, 2 is Western Norway Regional Health Authority, 3 is Central Norway Regional Health Authority and 4 is Northern Norway Regional Health Authority. The numbers are standardised in relation to persons in each health region, found at SAMDATA (39) and multiplied with 100,000. Actual use of TNF-inhibitors after health region is presented in table v4 in the appendix.

Use of home medication in relation to total use of TNF-inhibitor in region South-East was 35.8 percent home medication, followed by Western region with 42.8 present and Central and Northern used respectively 35.7 percent and 29.6 percent.

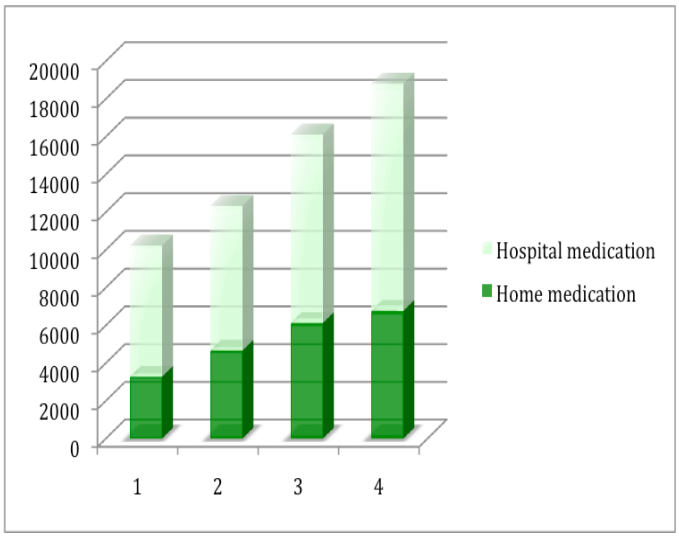


Figure 10 presents the use of TNF-inhibitors over time.

The horizontal axis presents year where 1 is 2004, 2 is 2005, 3 is 2006 and 4 is 2007. The vertical axis shows number of patients that have received TNF-inhibitors. Total consumption increased from 2004 to 2007 for both home- and hospital medication. When it comes to the the distrebution of home medication in relation to total use of TNF-inhibitors, it was lowest in 2004 (32.06 percent) and highest in 2006 (38.0 percent). Actual use from 2004 to 2007 may be found in the appendix in table v5. In relative sizes use of home medication increased from 2004 to 2006, and decreased from 2006 to 2007 with 5.18 percent.

6.3 Effects of the reform

Proportion of the variance in the dependent variable explained by the variance in the independent variables R^2, varies in the models from 0,211 to 0,320.

As an example, the estimates for share 20-66 (model 1) may be interpret as: When the percentage in age group 20-66 increases with one unit, the consumption of home medication will increase with 0,2 percent. The star represents the significance level respectively at 0.01-, 0.05- and 0.10 percent level. As an example, when the variable unemployed is not significant in model 1 this means that the probability is less than the significance level, then the hypothesis is rejected and the outcome is said to be statistically significant. The lower the significance level, the more the data must diverge in order to be significant. Therefore, the 0.01 level is more conservative than the 0.10 level (11).

The hypothesis tested where the change in the financial responsibility, and thereby relative prices, will lead to a shift from home medication to hospital medication. Further the hypothesis regarding the supply level is an assumption of that higher the supply of specialists in rheumatology, the more patients will receive treatment. Next we have assumed that patients with long travel distance to hospitals will to a higher degree then people with short travel distance prefer home medication, while high age (pensioners), due to that people in this group often have more available time then persons that work, additionally is the assumption that persons in age group 20-66 will increase the use of home medication. In addition to this specific hypothesis we test out effects of variables describing needs at municipality level, such as age structure, number of disabled and level of education.

6.3.1 Probability of receiving home medication

Among the share of patients receiving home medication there are stable and negative effects in both models of the variables reform and income. The negative reform variable may be interpreted as follows: after the financial reform, use of home medication decreased. This is in line with what we predicted, and also what we can see from figure 10. Relative, use of home medication increased from 2004-2006, and decreased from 2006-2007 with 5.18 percent. The hypothesis H1 is confirmed. The changed financial responsibility led to a shift from home medication to hospital medication, due to a change in relative prices.

Moreover, patients that live in a local government where the income level is high have a lower probability of receiving home medication. There were no significant effects of the trend variable, age group 20-66 and 67-80+. Share specialists are significant in the models, however it has a negative effect in model 1 and positive effect in model 2. This effect was expected to be indistinct, due to that the hypothesis regarding supply of rheumatologist expected a higher use in general.

Table 7, explanations on variation in consumption of TNF-inhibitors (2004-2007) Estimates from regression (standard error in brackets). Estimates for Hospital-dummies are reported in table v6 in the appendix.

	Model 1 **Share home medication**	**Model 2** **Log Share home medication**	**Model 3** **Total Consumption**	**Model 4** **Log - Total consumption**
Constant	0,636*	1.136	-0,008***	-9,363***
	(0,329)	(0,841)	(0,002)	(1,163)
Trend	0,014	-0,003	0,000***	0,205***
	(0,010)	(0,024)	(0,000)	(0,034)
Reform	-0,071**	-0,119**	-6,777E-6	-0,161**
	(0,023)	(0,056)	(0,000)	(0,079)
Gross income	-6,580E-7**	-1,693E-6**	7,385E-9***	1,635E-6
	(0,000)	(0,000)	(0,000)	(0,000)
Avs_Rauma	9,497E-5	0,001***	-5,863E-7	0,000
	(0,000)	(0,000)	(0,000)	(0,017)
Share_education	-0,005**	-0,007	4,913E-5***	0,031***
	(0,002)	(0,005)	(0,000)	(0,007)
Age	-0,128***	-0,010	Not included	Not included
	(0,012)	(0,033)		
Share 20_66	0,004	-0,018	7,595E-5**	0,012
	(0,005)	(0,013)	(0,000)	(0,018)
Share 67_80+	-0,004	-0,008	7,417E-5***	0,039***
	(0,004)	(0,009)	(0,000)	(0,013)
Share_spes	-0,033**	0,113**	9,497E-5	0,291***
	(0,016)	(0,043)	(0,000)	(0,058)
Share_ disabled	0,017**	0,018	-2,612E-5	-0,048**
	(0,006)	(0,014)	(0,000)	(0,020)
Share_unemployed	0,004	-0,085**	-3,051E-5	-0,042
	(0,013)	(0,034)	(0,000)	(0,047)
"Fixed effects"	YES	YES	YES	YES
Model fit (R2)	0,291	0,320	0,205	0,211

* p-value < 0,10 **p-value <0,05 ***p-value <0,01

There are however vague effects of travel distance, which is positive in model 2 and not significant in model 1. When gross income is left out of, the analysis shows that travel distance becomes significant and positive in model 1. This can be explained through the fact that local governments with high-income level often are in cities, or nearby cities, and therefore have a shorter travel distance to hospitals. They are correlated at level –0.352. The positive effect of travel distance may indicate that when a patient's distance from the hospital increases, the probability of receiving home medication increases. This is in line with what we predicted from hypothesis H4, we can say that patient's preferences is taken into account when the physician choose pharmaceutical.

The impact of education, disabled and unemployed are less clear in the model. On the one hand, the share of unemployment level reduces the probability of receiving home medication. On the other hand, the share of disabled patients has a higher probability for receiving home medication. Unemployed reduces the probability of receiving home medication this can be due to that unemployed patients often have more available time then persons that work. When it comes to disabled the fact can be that disabled persons need more assistance, and therefore receive more hospital medication.

The effect of the included hospitals as fixed effects, are represented in the appendix table v6. The dummy variables must be interpret in relation to the HF who had a consumption closest to the national average in the period, after controlling for other factors. Norlandssykehuset presents the national average, and are the reference category. Measured like this, the consumption of home medication was under the national average in the hospitals Betanien, Bergen, Ålesund, St. Olavs Hospital and UNN. The consumption was above the national average in the hospitals Lillehammer, Stavanger and Haugesund.

6.3.2 Probability of receiving TNF-inhibitors

Model 3 and 4 show the probability for patients to receive TNF-inhibitors. There are significant and positive effects of the time trend variable, income, education and share age group 67-80+. Significant and negative effects can be found from the variable reform. There are on the other hand, no significant effects of the unemployed and indistinguishable effects of the other variables.

The positive trend variable indicates that consumption and use of TNF-inhibitors increases over time, which is in line with what was found from figure 10. The negative effects of the reform variable in model 4 may indicate that the consumption has flattened over time.

If one look at the actual use of TNF-inhibitors from 2004-2007 presented intable v5 in the appendix, we find that actual use of TNF-inhibitors increased with 21 percent from 2004 to 2005, 30 percent from 2005 to 2006, and 17 percent from 2006 to 2007. This can be due to many reasons, but one possible might be that a one has reached the limits of who shall receive TNF-inhibitors.

Figure 9 also indicates that the region in North, that has the highest degree of rural areas, uses the highest share of hospital medication.

The positive effects of education and income in model 3 show that patients who live a local government where the average education and income level is high, have a larger probability of receiving TNF-inhibitors. Due to the fact that these patients are educated and wealthy, they turn to the knowledge about health and translate this into practice. The positive effects for age group 67-80+ indicate that as a larger share of persons in the age group 67-80+ living in the local government, the probability for receiving TNF-inhibitors increases.

The effects of the included hospitals as fixed effects are represented in the appendix table v6. The dummy variables must be interpret in relation to the HF who had a consumption closest to the national average in the period, after controlling for other factors. Norlandssykehuset presents the national average, and are the reference category. The effects presented in model 3 and 4 show that consumption of TNF-inhibitors is significantly higher on the folloeing hospitals: Buskerud, Betanien, Bergen, Ålesund and UNN. Buskerud and Betanien are belonging to region South-East, Bergen belongs to region West, Ålesund in the Central region and UNN is in Northern region. Since the estimate for UNN is the highest, and it is significantly higher than Norlandssykehuset it may indicate that the Northern region has the highest consumption of TNF-inhibitors.

7. Conclusion

The starting point for the research was first analysing if the change in the financial responsibility had influenced consumption and use of TNF-inhibitors. The focus of the paper was: (1) if changes in relative prices as follows from transferring of the financial responsibility affect use of home- versus hospital medication and (2) if transfer of the financial responsibility from NSI to RHF, and with that from a reimbursement system to a system partly based on block grants, have affected the total number of users.

The basic assumption is this analysis is that physicians are decision makers, and act as the patient's agents. According to relative prices, supply side characteristics as the hospitals revenue level, or number of specialists in rheumatology and factors on the demand side as the patients travel distances to hospitals and their age, we assumed that the hospitals prioritize between home- and hospital medication. Changes in relative prices was of particular interests, due to the fact that the reimbursement from NSI could before the financial change been seen as a subsidy to the hospitals that affected the relative prices the hospital had to pay for home medication. When the financial responsibility was transferred, this subsidy disappeared and we assume that as the relative prices on home medication increased this will thereby lead to a shift from home medication to hospital medication. From the supply side we assumed that number patients that receive treatment would increase parallel with the supply of specialists. When it comes to patients' preferences we assumed that increased travel distance would increase the use of home medication, and the opposite for age, that high age would increase use of hospital medication. Last we tested out effects of variable that described need at local government level, such as number of disabled and education. From these variables we did not have any specific hypothesis.

From the regression the hypothesis regarding the reform are confirmed. There are clear effects of the reform that is; the probability for receiving home medication has decreased after implementation of the financial regime in 2006. The relative use of home medication increased until 2006, and decreased from 2006-2007 with 5.18 percent. There are however quite large differences between regions, and it seems like patients in areas in Northern Norway have a lower probability of receiving home medication than others. This is also the conclusion from figure 9, where the distribution of TNF-inhibitors in regions is presented, and Northern Norway uses the relative lowest amount of home medication, thus highest on

hospital medication in the four regions. Also the proportion of home medication and hospital medication varies quite much between regions. The same results are found among the fixed effects presented in table in table v6.

The transferring of the financial responsibility has affected numbers of patients receiving TNF-inhibitors. The trend variable in model 3 and 4 show that numbers of users has increased from 2004-2007, and that total consumption somewhat has decreased from 2006 to 2007, due to the negative reform variable. This is also the conclusion we can draw from the actual numbers of users, where the growth from 2004-2005 was 21 percent, 2005 to 2006 30 percent, and last 2006-2007 17 percent, the actual growth is weaker from 2006-2007; this may be due to that the limits for who shall receive are about to be reached, or maybe stronger priorities as a consequence of the guidelines. This is thus a speculation, it is not possible to say anything tangible.

In model 3 and 4 education is positive in both models, but income is only positive in model 3. This may indicate that income has a less positive impact on receiving TNF-inhibitors than education. One might assume that people who live in local governments far from nearest hospital have a lower probability of receiving TNF-inhibitors, but the fact it opposite. The analysis reveals that people in Northern Norway have a larger probability of receiving TNF-inhibitors. There are however some support for lower use of home medication in Northern Norway, which is the region with the largest travel distances. Travel distance has a positive effect of receiving home medications, and not any effects of receiving TNF-inhibitors. This should somehow be positive for policy makers, due to that fact that there often are worries that long distance to the hospitals indicate poorer supply of services.

To sum up the main conclusion from this analysis it is that the reform variable has a negative effect in both model 1 and 2, and one may say that the probability of receiving home medication has decreased after the reform, and that relative prices may be the current factor when physicians choosing between the pharmaceuticals.

There are however some weaknesses with the study. In order to get a more accurate result, 2008 data should be included. The same applies for the analysis level. Optimal an analysis like this should have been done at an individual level, but due to time restrictions and the

fact that we could not get a licensing from the Data inspectorate, this was not possible. If this analysis should be done with individual data it would be interesting seeing if the individual data would be the same as the cells analysing here. In order to get a more precise effect of the reform, dummy variables could be coded for every year. One could also analyse community variables to see if there are differences between the regions. It could be interesting analysing why Northern Norway has a higher consumption than the other regions. A hypothetical reason can be that hospitals in Northern Norway may have greater capacity. The change in the financial responsibility was implemented 1 June 2006, and our dummy variables were coded as before this (2004-2006), and after (2007), but due to inertia effects this should not cause any problems. During the process it has come forward that the pharmaceuticals MabThera og Raptiva not was transferred before 1 January 2008. This will probably not cause any problems since it treats so few patients. It will therefore be recommended that further studies will include MabThera, but not Raptica because the marketing license was suspended February 19 2009.

The government transferred TNF-inhibitors among other because the different financing arrangements between home- and hospital medication has led to that choice of pharmaceutical had largely been based on economic and not medical reasons, and that hospital physicians have the best opportunities to make appropriate priorities in the treatment of patients with these pharmaceuticals compared to other treatment. Hospital physicians will get an improved basis for the priority when funds are transferred. As the results show, there has been a shift from home medication to hospital medication. The result may indicate that number of users is lower after the reform, which again may indicate that when the financial responsibility was transferred and the hospital physician got all the responsibility, the use has decreased due to the fact that hospitals physicians may have offered other efficient treatment.

We can with certainty say that there has been a shift from home medication to hospital medication as a result of the reform after the implementation of the financial arrangement. However, one should explore the patterns in more details with individual data in order to identifying some underlying mechanism before suggesting specific reforms of investigation.

8. References

1. LMI. Fakta og tall 2009. Legemidler og helsetjenester. 2009.

2. St.prp.nr.1. For budsjettåret 2006. In: Omsorgsdepartementet H-o, editor. Oslo; 2005-2006.

3. LMI. Tall og fakta 2008. 2008 [updated 2008; cited 2009 29.01]; Available from: http://www.lmi.no/tf/2008/tall_og_fakta_2008.pdf

4. St.prp.nr.1. For budsjettåret 2008. In: omsorgsdepartemenet H-o, editor. Oslo: www.regjeringen.no; 2008.

5. Walsh JESCE. Prinsiples of microeconomics. W.W. Norton & company, Inc.; 2002.

6. St.prp.nr.1. For budsjettåret 2009. 2008-2009.

7. NAV. Egenandeler. 2009 [updated 2009; cited 2009 09.02]; Available from: http://www.nav.no/page?id=354.

8. Ot.prp.nr.83(2001-2002). Om lov om endring i folketrygdloven (finansiering av visse legemidler). In: Omsorgsdepartementet H-o, editor. Oslo; 2002.

9. St.prp.nr.1. For budsjettåret 2007. In: Omsorgsdepartementet H-o, editor. Oslo; 2006-2007.

10. Lundin D. Moral Hazard in physician perscription behavior. Journl of Health Economics. 2000;19.

11. Eikemo TAC, Tommy Høyvarde. Kvantitav analyse med SPSS. Tapir Akademisk forlag; 2007.

12. Wyeth. Revmatiker guiden. Wyeth AB 2008 [updated 2008; cited]; Available from: http://www.revmatikerguiden.no/(S(qhwiki45oevwgwfp1ks0fhq5))/Default.aspx?PagId=23.

13. Arentz-Hansen Hea. TNF-hemmere ved revmatiske sykdommer elektronisk ressurs. Oslo: Nasjonalt kunnskapssenter for helsetjenesten; 2006.

14. Kvien TKH, M.S.; Kaufmann. C.; Mikkelsen, K.; Nordvåg B.Y.; Rødevand E. A Norwegian DMARD register: Perscription of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clinical and experimental rheumatology 2005. 2005;23:s188-s94.

15. Clinic C. Inflammation: What do you need to know. The Cleveland Clinic; 1998 [updated 1998; cited 2008 14.08]; Available from: http://my.clevelandclinic.org/symptoms/inflammation/hic_inflammation_what_you_need_to_know.aspx.

16. Haug EB, Jan G.; Sand, Olav; Sjaastad, Øystein V. Menneskekroppen fysiologi og anatomi. 2. utg. ed. Oslo: Gyldendal akademisk; 2006.

17. Diakonhjemmet. Pasientinformasjon om ravmatiske sykdommer. Diakonhjemmet sykehus; 2009 [updated 2009; cited 2009 13.01]; Available from: http://www.diakonsyk.no/modules/module_123/proxy.asp?D=2&C=530&I=5350.

18. Eriksen M. Barneleddgikt (Juvenil idioplastisk artritt). Oslo: Rikshospitalet; 2007 [updated 2007; cited 2009 20.01]; Available from: http://www.rikshospitalet.no/ikbViewer/page/no/pages/sykdom/diagnoser?p_menu_id=32169&p_sub_id=32163&p_style_id=32184&p_doc_id=58528.

19. Eriksen M. Bekhterevs sykdom. Rikshospitalet; 2007 [updated 2007; cited]; Available from: http://www.rikshospitalet.no/ikbViewer/page/no/pages/sykdom/diagnoser?p_sub_id=32161&p_style_id=32182&p_doc_id=40604&p_prev_id=23333.

20. Næss O. Sykdomslære og patologisk anatomi. Nesbru: Vett & Viten A/S; 2002.

21. Coll Pea. Nasjonale faglige retningslinjer for bruk av TNF-a hemmere og andre biologiske betennelsesdempende legemidler innen revmatologi, gastroentologi og dermatologi. In: helsedirektoratet S-o, editor. Oslo; 2007.

22. Holen S. Tarmsykdommene Ulcerøs kolitt og Crohns sykdom. Oslo: Rikshospitalet; 2008 [updated 2008; cited 2009 20.01]; Available from: http://www.rikshospitalet.no/ikbViewer/page/no/pages/sykdom/diagnoser?p_menu_id=32169&p_sub_id=32161&p_style_id=32182&p_doc_id=64299.

23. Gigtforeningen. Biologiske lægemidler. Gigtforeningen; 2008 [updated 2008; cited]; Available from: http://www.gigtforeningen.dk/viden+om+gigt/medicin/biologiske+lægemidler.

24. Håkonsen H. Legemiddeløkonomiske tiltak for å begrense veksten av sammfunnets legemiddelkostnader i perioden 1998-2004. Har norske myndigheters tiltak virket etter hensikten? Oslo: University of Oslo; 2005.

25. Brekke KS, Odd Rune Pris- og avanseregulering i legemiddelmarkedet Stein rokkan senter for flerfaglige samfunnsstudier. 2003;20.

26. Dalen DM. Legemiddelmarkedet etter apotekreformen. Helseøkonomisk forskning. 2003;2003:11.

27. Johnsen JR. Health systems in Transition. European Observatory on health systems and policies; 2006.

28. Regjeringen. Legemidler. Helse- og omsorgsdepartementet; 2009 [updated 2009; cited 2009 21.01]; Available from: http://www.regjeringen.no/nb/dep/hod/tema/Legemidler.html?id=11633.

29. Folland SG, Allen ; Stano, Miron The Economics of Health and Health care. Pearson Education; 2007.

30. Regjeringen. Regulering av priser i legemiddelmarkedet. 2009 [updated 2009; cited 2009 03.02]; Available from: http://www.regjeringen.no/nb/dep/hod/tema/Legemidler/regulering-av-priser-i-legemiddelmarkede.html?id=449422&epslanguage=NO.

31. St.meld.nr.18. Rett kurs mot riktig legemiddelbruk. In: omsorgsdepartementet H-o, editor. Oslo; 2004-2005.

32. LIS. LIS - Senter for avtaler om kjøp av legemidler for helseforetakene i Norge. 2009 [updated 2009; cited 2009 03.02]; Available from: http://www.lisnorway.no/sider/tekst.asp?side=1&meny=Om%20oss&undermeny=true.

33. Halsteinli VSOOHTTPH. Allocation of labour to somatic and psychiatric spesialist care-The effects of earmarked grants. 2005.

34. Dalen DMS, Steinar ; Haabeth, Tonje. Price regulation and generic competition in the pharmaceutical market. Hero. 2006;2006:1.

35. NOU(2008:2). Fordeling av inntekter mellom regionale helseforetak. In: omsorgsdepartementet H-o, editor. Oslo: Norges offentlige utredningen; 2008.

36. Kindseth OKS. SAMDATA SYKEHUS. sykehusforskning SNif, editor.; 1996.

37. Folkehelseinstituttet. Reseptregisteret, Definisjoner. Oslo: Folkehelseinstituttet; 2009 [updated 2009; cited 2009 15.04]; Available from: http://www.reseptregisteret.no/Detaljer.aspx.

38. Nerland SMTPH. Forbruk av spesialisthelsetjenester, Ble det større likhet etter sykehusreformen? Universitetsforlaget, Tidsskrift for samfunnsforskning. 2006.

39. Jørgenvåg R. SAMDATA Somatikk sektorrapport 2005. SINTEF rapport. 2005.

9. Appendix

Table V1, DRG coding

Out-patient treatment/day-treatment:		
Main diagnosis	Infusion code :	Z51,2
	Disease diagnosis	DRG-code
Second diagnosis:	RA	M05,8/M06,0
	Juvenil RA	M08,0
	BD	M45
	PSA	M07,3/L40,5
	Other M codes, (connective tissue diseases/ Vacuities)	M32-M35
Inpatient treatment: opposite coding thus,	Main diagnosis = disease diagnosis	
	Second diagnosis = infusion code	
	These patients will be placed in DRG 240/241	

Table V2, ID for hospitals

1	Sykehuset Østfold HF
2	Martina Hansens Hospital
3	Diakonhjemmet/Rikshospitalet
4	Sykehuset Innlandet HF (Kongsvinger)
5	Revmatismesykehuset AS - Lillehammer
6	Sykehuset Buskerud HF
7	Betanien Hospital
8	Sørlandet Sykehus HF
9	Stavanger Universitetssykehus HF
10	Revmatismesykehuset, Haugesund AS
11	Haukeland Sykehus
12	Helse Førde HF Sentralsjukehuset
13	Ålesund sykehus
14	St. Olavs Hospital HF
15	Helse Nord-Trøndelag HF
16	Norlandssykehuset
17	Universitetssykehuset i Nord-Norge HF (UNN)

Table V3, actual use of home medication and hospital medication after Hospital ID

Hospital ID	Home medication	Hospital medication
1	926,03	1091
2	2643,33	2282
3	1558,41	2345
4	784,44	813
5	527,03	395
6	949,38	5411
7	1908,3	5379
8	937,7	609
9	1455,15	257
10	499,72	75
11	2358,23	6085
12	711,96	305
13	935,75	2377
14	958,82	1641
15	1047,1	1288
16	1933,75	2710
17	714,08	3584

Table V4, actual use of TNF-inhibitors after health region

Health region	Home medication	Hospital medication	Sum
South East	10234,62	18332	28559,62
West	5025,06	6722	11747,06
Central	2941,67	5306	8247,67
Northern	2647,83	6294	8941,83

Table V5, actual use of TNF-inhibitors from 2004 to 2007

Year	Home medication	Hospital medication	Sum
2004	3282,04	6952	10234,04
2005	4668.14	7665	12333,14
2006	6129,7	9985	16114,7
2007	6769,67	12045	18814,67

Table V6. Explanation on variation in use of TNF-inhibitors

"Fixed effects"	Model 1 Share home medication	Model 2 Log Share home medication	Model 3 Total consumption	Model 4 Log Total consumption
Sykehuset Østfold	0,023 (0,039)	0,087 (0,096)	0.000** (0.000)	-0,571*** (0,102)
Martina Hansens sykehus	0,014 (0,040)	0,079 (0,098)	-5,243E-5 (0.000)	-0,080 (0,100)
Diakonhjemmet	-0,031 (0,099)	0,020 (0,226)	0.000* (0.000)	-0,432* (0,249)
Helse Innlandet (Kongsvinger)	-0,009 (0,036)	0,062 (0,089)	0.000*** (0.000)	-0,485*** (0,095)

Revmatisme sykehuset Lillehammer	0,067*	0,175**	0.000***	-0,680***
	(0,035)	(0,086)	(0.000)	(0,090)
Sykehuset Buskerud	-0,378***	-1,247***	0.001***	0,849***
	(0,037)	(0,096)	(0.000)	(0,094)
Betanien	-0,230***	-0,600***	0.001***	0,575***
	(0,032)	(0,079)	(0.000)	(0,082)
Sørlandet	0,058	0,095	0.000	-0,496***
	(0,037)	(0,089)	(0.000)	(0,095)
Helse Stavanger	0,432***	0,568***	0.000	-0,572***
	(0,051)	(0,122)	(0.000)	(0,129)
Raumatismesykehuset Haugesund	0,306***	0,552***	0.000*	-0,685***
	(0,059)	(0,142)	(0.000)	(0,149)
Helse Bergen	-0,169***	-0,518***	0.001***	0,390***
	(0,036)	(0,090)	(0.000)	(0,093)
Helse Førde	0,122**	0,113	0.000	0,081
	(0,039)	(0,097)	(0.000)	(0,101)
Ålesund	-0,225***	-0,573***	0.000**	0,217**
	(0,033)	(0,083)	(0.000)	(0,084)
St. Olav hospital	-0,124***	-0,210**	1,297E-5	-0,154
	(0,035)	(0,090)	(0.000)	(0,091)
Helse Nord-Trøndelag	0,034	-0,124	0.001***	0,101
	(0,037)	(0,090)	(0.000)	(0,096)
UNN	-0,364***	-1,152***	0.003***	0,939***
	(0,029)	(0,074)	(0.000)	(0,074)
Norlandssykehuset	Reference category	Reference category	Reference category	Reference category

* p-value < 0,10 **p-value <0,05 ***p-value <0,01